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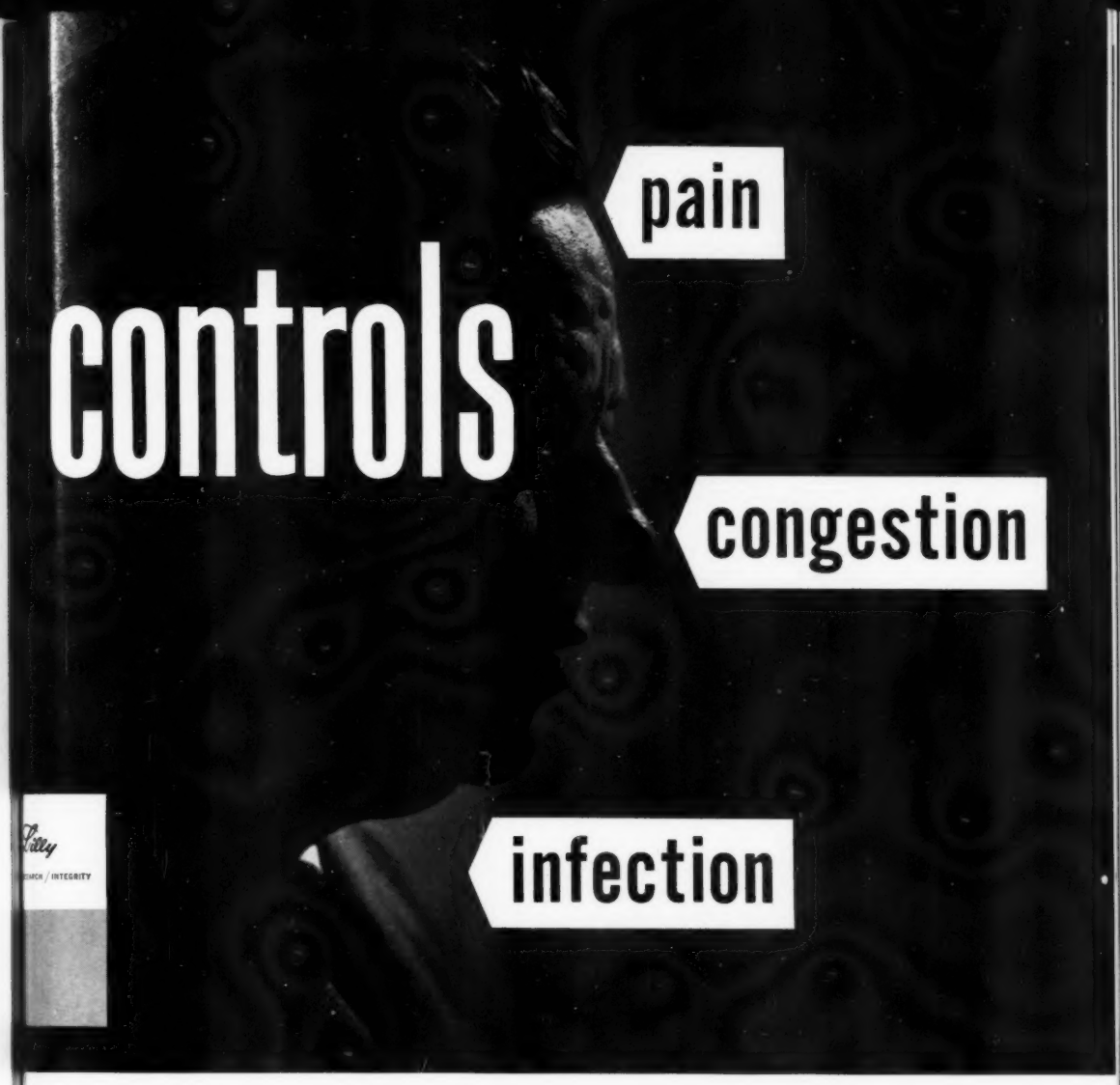

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• APHTHOUS STOMATITIS

Q. A 21 year old woman has had aphthous stomatitis of the buccal mucosa and tongue since August 1958. A high-vitamin nutritional supplement, administered for three months, was not effective, and a course of penicillin troches gave only temporary relief. Associated gastrointestinal symptomatology has not been noted. Please recommend further treatment.

M.D.—Pennsylvania

A. Chronic aphthae of the mouth continue to plague physicians and dentists. The specific causation is not known. Occasionally, foods such as English walnuts, strong cheese and chocolate have given rise to aphthae. The frequent occurrence of aphthae in the presence of emotional stress and, at times, gastrointestinal disturbance, suggests a causative association. Certainly, when aphthae are found, the teeth and methods of oral hygiene should be examined to be sure that no initiating trauma is present.

Supportive treatment, with symptomatic relief, is the usual therapeutic regimen. The greatest difficulty arises when the lesions become secondarily infected. Some of the mild escharotic agents, if used early enough and if applied only to the developing ulcer, may limit extension of the disease. Topical anesthetic agents frequently allow persons afflicted with aphthae to eat comfortably, and an antihistaminic preparation held in the mouth will act as a mild obtundent. Autohemotherapy has not given particularly satisfactory results. Some of the cortisone ointments have been used locally, and attempts have been made to alter the oral flora by the use of antibiotic, bacteriostatic or bactericidal agents and lactobacillus tablets.

• PYURIA

Q. A patient who has had pyuria for 10 to 12 years was operated on a year ago for bilateral stag-horn calculi. A recent culture of the urine showed a growth of *Pseudomonas aeruginosa*, which has proved resistant to antibiotic and sulfonamide therapy. What treatment would you advise?

M.D.—Pakistan

A. In a case such as this, one must be sure that no interference with the drainage of urine from the kidneys is present. When obstruction occurs at the ureteropelvic juncture, it frequently is bilateral. I would make certain that the foci of infection were eradicated and would acidify or alkalize the urine, depending on the pH at the time the stones were found. If the infection is not easily controlled, pelvic lavage may be used. Stones of this character in the kidneys would seem to indicate that there are probably many small ones and that re-formation will occur frequently.

Second consultant: A postoperative roentgenogram of the urinary tract should be made to ascertain whether any recurrent calculi are present. A urogram also should be made in a search for hydronephrosis. If there are no indications of either recurrent calculi or hydronephrosis, the ureters should be catheterized and the urine collected from the kidneys for culture; if the *Pseu-*

(Continued on page A-20)

better safe than sorry

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domonas is coming from the prostate or urethra rather than from the kidneys, it is probably of no consequence.

If the patient has no calculi, I would ignore the *Pseudomonas* and confine the treatment simply to forced fluids. If recurrent calculi are present, in addition to forced fluids the patient may be given 1 oz. of BASALJEL® after each meal and at bedtime in order to diminish the excretion of phosphates. If constipation develops, the Basaljel may be alternated with MAALOX®, which probably will rectify this difficulty.

• AMEBIC HEPATITIS

Q. Please describe the pathologic picture of amebic hepatitis without jaundice.

M.D.—New Jersey

A. The pathologic picture of amebic hepatitis without jaundice is not easy to describe. In fact, there are differences of opinion as to whether or not such a condition actually exists.

If one is willing to accept the view that *Entamoeba histolytica* trophozoites travel from the intestines to the liver, then during a period which occurs approximately one month after the initial parasitic infection there may be a clinical condition of amebic hepatitis. At this time the patient may run a fever of 100 to 101° F., and he may be slightly jaundiced. There is a vague type of gaseous distention, abdominal discomfort and bloating, and on physical examination the liver is slightly enlarged and almost invariably tender. Percussion and palpation of the liver on the right side produce severe pain, and liver function studies may indicate parenchymal disease. By the time these symptoms appear, the parasites may have disappeared from the intestines and may not be present in the stools. Within a few weeks after this picture of amebic hepatitis appears, the organisms coalesce into a liver abscess, and other complications of amebic dysentery may occur.

• TRAUMATIC BRONCHITIS

Q. Is there any cause other than aspiration for traumatic bronchitis? In an automobile accident four months ago, a 57 year old man fractured his fourth, fifth and sixth ribs at about the posterior axillary line on the left side. There was no separation of fragments. One day after the accident, bronchitis developed on the left side and spread to the right side. The bronchitis is extensive and diffuse, and it has not responded to the usual treatment. A roentgenogram of the chest shows no pleural or bronchial thickening. What treatment would you suggest?

M.D.—New Jersey

A. Trauma to the bronchus may occur after crushing injuries to the wall of the chest. The bronchus actually may rupture after such an injury, although this is rare. When this occurs, atelectasis of the lobe or of the entire lung usually results. The diagnosis is made by bronchoscopic examination, at which time evidence of a blood clot or granulation tissue is seen, with varying degrees of obstruction of the bronchus. Aspiration pneumonitis may occur after any type of accident in which the patient has become unconscious or in which there has been vomiting with aspiration of gastric contents. After trauma to the chest, it is also possible for varying degrees of atelectasis to develop as a result of reduction in movements in the thoracic wall during respiration. Reduction of such movements occurs because of the considerable pain caused by breathing. When these circumstances develop there may be retention of the patient's bronchial secretions, followed by atelectasis.

One treatment is to encourage the patient to cough and to raise his secretions, regardless of the pain thus produced. If this is not effective, bronchoscopy often is necessary. Sometimes, it is advisable to perform a tracheotomy so that the patient's secretions may be aspirated.

• BLOODY AMNIOTIC FLUID

Q. What are the probable causes of bloody amniotic fluid?

M.D.—Pennsylvania

A. Bloody amniotic fluid results from a rupture of the vessels on the fetal surface of the placenta or of the vessels of the umbilical cord. Varicosity of these vessels, trauma, or congenital thinness and fragility must be considered. Spontaneous or traumatic rupture of the surface vessels of the fetus, such as in hemangiomas or meningoceles, also may cause loss of blood into the amniotic fluid. Because the source of amniotic fluid is not known with certainty, other conditions of which we are not aware might produce this result.

What's happening in Medicine ?

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

CAUSE OF CRIB DEATHS CITED

American Society of Clinical Pathologists and College of American Pathologists:

- Sixteen (84 per cent) of 19 consecutive cases of sudden death in infants and children were caused by endomyocardial fibrosis. The condition does not show up if the autopsy is delayed even slightly or if the heart is exposed to the atmosphere. Mechanical suffocation in crib deaths should not be diagnosed unless the evidence is conclusive and findings at autopsy exclude the possibility of endomyocardial fibrosis.—Dr. Louis Goodman, South Side Hospital, Pittsburgh.
- The number of paternity cases tried in the courts of New York rose 250 per cent in five years. Ten per cent of the accused men denied the charge. About one-half of these were acquitted by trial, 40 per cent because blood grouping excluded them.—Dr. Leon H. Sussman, Beth Israel Hospital, New York.
- A fluorescent antibody technic enables the diagnosis of yellow fever to be confirmed within 24 hours instead of within a week or longer after onset of infection.—Dr. H. F. Smetana, Armed Forces Institute of Pathology, Fort Detrick, Md.

ANEMIA IN PREGNANCY

American Association of Obstetricians and Gynecologists:

- When anemia due to retarded erythrocytopoiesis is encountered during pregnancy, the cause is rarely pregnancy per se. This condition usually is caused by either a deficiency of one or more erythrocytopoietic agents or an associated disease which results in depression of bone marrow.—Dr. Jack A. Pritchard, University of Texas Southwestern Medical School, Dallas.
- Unexplained vaginal bleeding is more serious when it occurs in the midtrimester than when it occurs in the last three months of pregnancy.—Dr. Gordon W. Douglas, New York University College of Medicine, New York.

GENETICS AND INFARCTS

Genetics Society of America:

- Genetic factors may be responsible for 10 to 15 per cent of all myocardial infarcts, particularly those associated with hyperlipemia.—Dr. Kurt Hirschhorn, New York University Post-Graduate Medical School, New York.
- Diabetes appeared to develop at an early age more often in siblings of juvenile diabetics than in other diabetics in a comparable random series. However, the diabetic children of persons who were juvenile diabetics were not similarly affected.—Dr. Nancy E. Simpson, Hospital for Sick Children, Toronto, Canada.

BEEF FILM AS BURN DRESSING

Clinical Congress, American College of Surgeons:

- A new biologic dressing, regenerated beef collagen film, has been evaluated for its effectiveness in treating skin defects in mice. Use of the film for treating extensively burned patients is considered a clinical possibility.—Drs. G. W. Hyatt and A. M. Pappas, United States Naval Medical School, Bethesda.
- Use of a prosthesis made of TEFLON® to bridge defects in the common bile duct produced excellent results in 15 of 19 animals. There was no evidence of obstructive jaundice or secondary cholangitis in any of the surviving animals.—Dr. David Kramish, University of Colorado School of Medicine, Denver.
- Selective impregnation of gallstones and stones of the common bile duct with radioactive rose bengal 24 to 72 hours before surgery has been shown to be feasible. There is an affinity for those stones that have a surface composition of bilirubin.—Dr. Colin G. Thomas, Jr., University of North Carolina School of Medicine, Chapel Hill.

POWER SEEKERS HARM CHILDREN

American Psychological Association:

- The age-old conflict of who is to "wear the pants" in the family is a factor in producing mentally disturbed children. The least conflict is found when neither parent has an intense need to dominate the family.—Dr. Marvin Zuckerman, Indiana Institute of Psychiatric Research, Indianapolis.
- Chlorpromazine hydrochloride was found to be somewhat more effective than was reserpine in treating mental disorders. Both drugs proved superior to no medication at all.—Drs. Donald R. Gorham and John R. Shawver, Veterans Administration Center, Waco, Tex.

QUALITIES OF "REAL" SCIENTIST

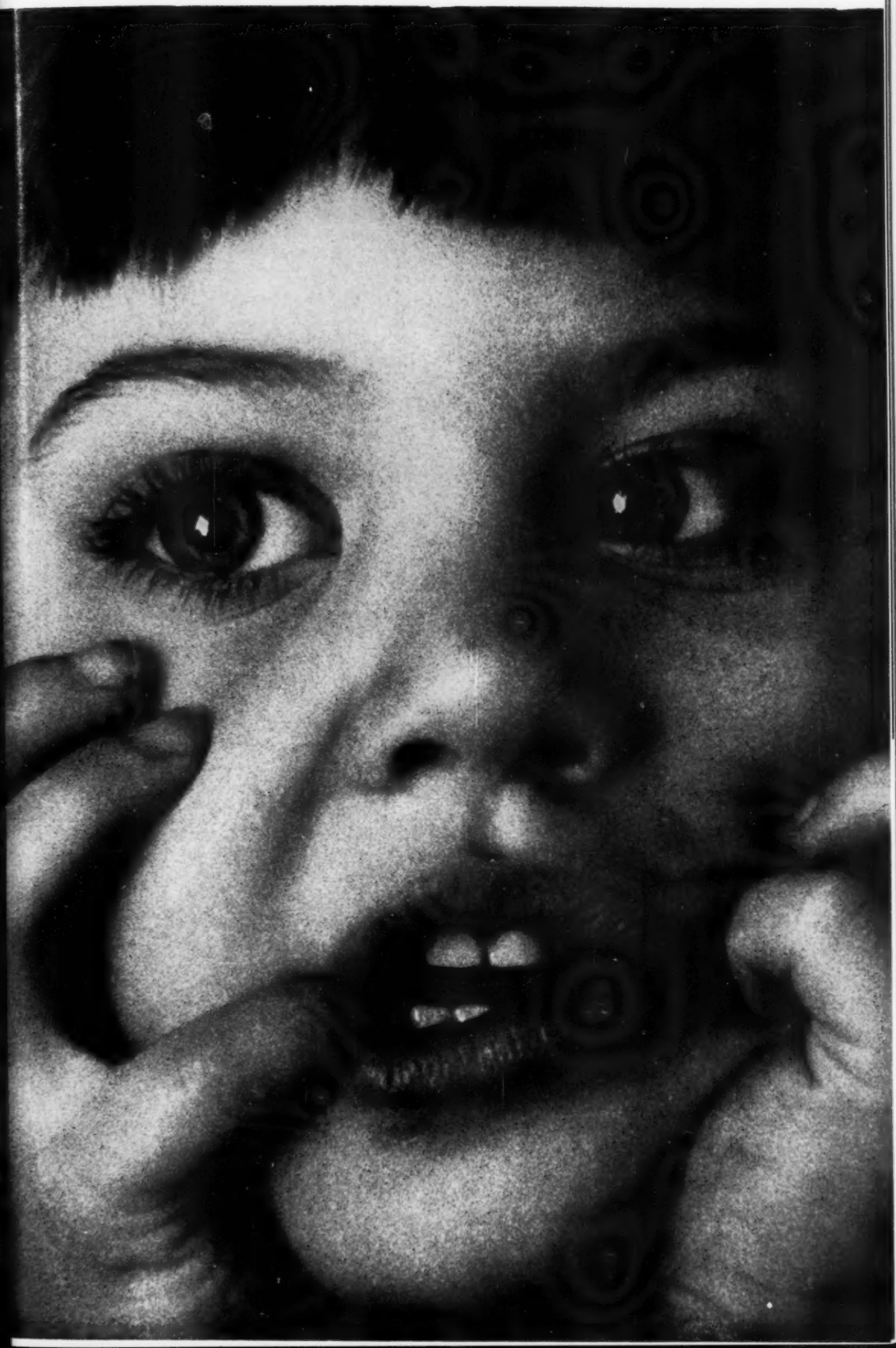
Second World Conference on Medical Education:

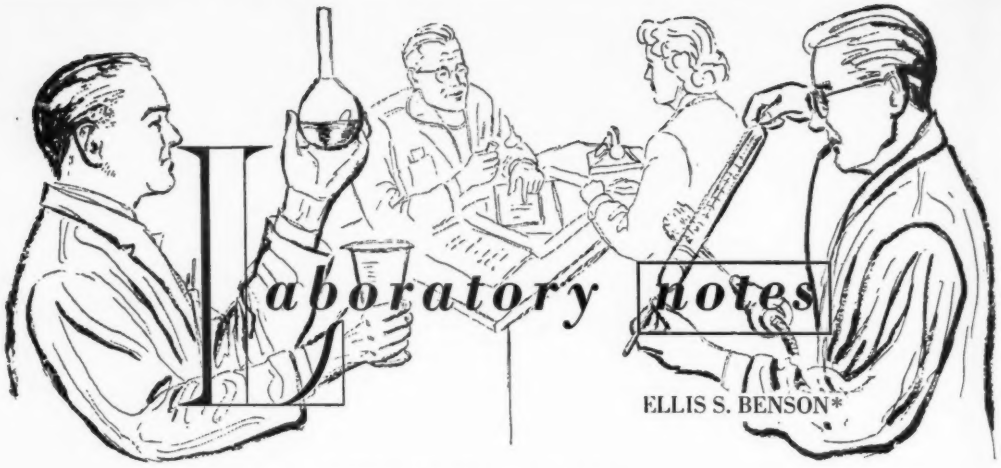
- A real scientist is one who dedicates himself to original research, i.e., the search for new facts still unknown and unexpected, which will show results. A scientist is not the ordinary follower or filer of facts which bring no results. His selflessness is deeper than his love of glory or pecuniary benefits. He is inspired by a great devotion to science. One of his greatest virtues is generosity; he has a deep and paternal willingness to aid students and a desire to assist research, hoping only for new findings and not caring to appear as author of such undertakings.—Dr. Bernardo A. Houssay, University of Buenos Aires, Argentina.

CIRCULATION SUPPORTED MECHANICALLY

Illinois State Medical Society:

- A closed system has been developed to obtain mechanical support of the circulation for a number of days, which might be necessary in severe coronary occlusion or in heart failure associated with a correctable heart lesion. The system takes one-half the blood returning to the heart and delivers it to the arterial system, bypassing the heart and lungs. The flow of venous blood is collected by gravity. Pumps return the blood to the arterial system via the thigh. The longest period of veno-arterial pumping in the human was 26 hours.—Dr. James F. Dickson, III, Presbyterian Hospital, Philadelphia.
- The antimicrobic agents, while not infallible, have stood the test of time. Real and lasting gains are evident in that many of the common bacterial infections are controlled over 90 per cent of the time. Almost all infections except those caused by viruses are treatable at least part of the time.—Dr. H. Mark Lepper, University of Illinois College of Medicine, Chicago.





Misuse of Blood Transfusion

WILLIAM H. CROSBY†

Walter Reed Army Medical Center, Washington, D. C.

The potential hazards of blood transfusion therapy—hemolytic reaction, transmission of disease, overtransfusion, etc.—have been quite frequently brought to our attention. One facet of this aspect of blood transfusion, in my opinion, has not been emphasized enough: careful adherence, or lack of it, to the proper indications for the prescription of blood for transfusion. I think the following article has cogency for all of us in the practice of medicine.—Ellis S. Benson, M.D.

A person would be liable for damages following and caused by a transfusion that was not indicated by the facts of the case. Even if no negligence could be proved . . . an action for damages would lie if the plaintiff could prove that the transfusion was not indicated medically."[1] Fortunately, this is an aspect of transfusion therapy with which few physicians and surgeons have had to deal. The proper use of blood transfusion, however, poses a problem, and many of us deserve criticism for the way in which we have met this problem. The reason for misuse of blood transfusions is that we are not sufficiently aware of the valid indications for this procedure. A surgical operation is not an indication for blood transfusion. Uterine bleeding is not an indication. Neither is a low hematocrit reading. Blood transfusion is not a tonic. It is not a placebo. It does not improve wound healing. Nor is it a substitute for careful consideration of the patient and his problem.

Setting aside the question of exchange transfusions, there are two valid indications for the transfusion of blood: (1) to improve the stability of the circulatory system when the blood volume has been reduced in such a way as to imperil the patient; (2) to improve the oxygen-carrying capacity of the blood to prevent acute hypoxia or invalidism.

During the Korean conflict the use of massive blood transfusions saved the lives of many of the most severely wounded soldiers. The blood was given rapidly in large amounts, 10 l. in an hour, 20 l. in a day. Critics, relying on so-called common sense rather than firsthand experience, declared that the surgeons in Korea used too much blood. The surgeon's problem was not, however, to answer such criticism but to re-establish and maintain the stability of the patient's circulatory system while he underwent the essential surgical pro-

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*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

†Chief, Department of Hematology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

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cedure. The criterion of an adequate transfusion was not established by any measurement of blood volume or hematocrit (although these were often done); nor was the resuscitative effort limited by a preconceived notion of the amount of blood it was *safe* to give. The surgeon was governed by the blood pressure, pulse rate, and ability of the severely wounded patient to withstand gentle manipulation, such as elevation of the shoulders.

Contrast this, if you will, with a surgical service at home where every patient undergoing major elective surgery receives a liter of blood the day before the operation to make sure he is not suffering from "chronic shock." (On such a service one patient with polycythemia received a liter of blood when his hemoglobin was 18 gm.) Contrast the Korean practice with that of obstetric services where every pregnant woman receives a transfusion when a laboratory report indicates that her hemoglobin concentration is less than 10 gm. Contrast the practice of our surgeons in Korea with that of a cancer service where once a week hematocrits are done and every patient with a reading below 38 per cent receives 1 unit of blood and every patient whose level is below 32 per cent receives 2 units. I have not invented these instances, and they are not exaggerated. They are flagrant examples of what might be called the secretarial practice of medicine. In such a practice a stenographer types out the laboratory request, and when the patient flunks her hemoglobin test the stenographer types out a transfusion request.

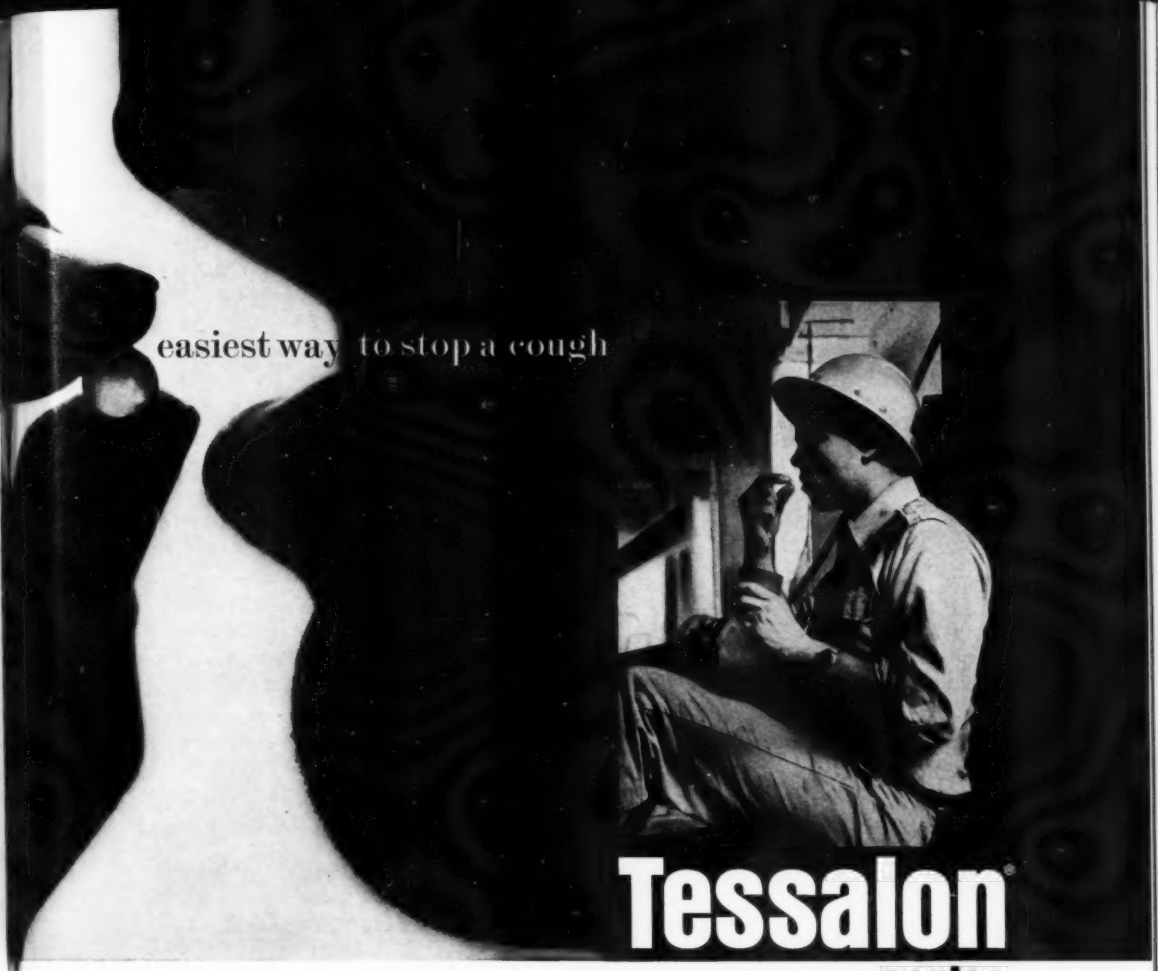
Several years ago at the Armed Forces Institute of Pathology all of the cases of acquired hemolytic anemia were reviewed. There were approximately 100 cases submitted by the Armed Forces, the Veterans Administration and civilian hospitals. Hemolytic anemia is a serious disease, and the mortality in the series was high. It was higher than it might have been, however, had not eight of the patients died because of inept use of the transfusion service. Five died of acute anemia; they had not received transfusions when they should have. Three died of complications of unnecessary transfusions: Two of these deaths were due to reactions; the third was caused by fulminating viral hepatitis three months after the so-called prophylactic transfusion of a unit of plasma during the course of an uneventful splenectomy.

All of us are concerned with the welfare of our patients. All of us are aware that we should not undertake a dangerous procedure without a thoughtful consideration of the indications and consequences and that blood transfusion is inherently dangerous. When we prescribe the transfusion we should balance the remote—although not less real—dangers against a present, real, even urgent, requirement of the patient. Anemia alone is not a sufficient justification. The requirement of the anemic patient for oxygen-carrying capacity should be balanced against his present capacity. Much of a person's 15 gm. of hemoglobin is a reserve against strenuous exertion. Where there is no requirement for exertion an individual can well tolerate a lower level of hemoglobin. For a sedentary life 10 gm. is often sufficient, and most bedfast patients are comfortable with as little as 5 or 6 gm. Many patients can learn to live with a chronic anemia, and a little quiet encouragement is often as helpful as repeated blood transfusions.

Acute blood loss must also be regarded with a critical judgment. A healthy adult can sustain the rapid loss of one-third of his blood volume without serious derangement of circulatory stability. Recently during the delivery of a child a woman lost by final actual measurement 700 ml. of blood. It is reasonable to suppose that she could have sustained this loss without danger and without transfusion. In fact, however, the blood loss was replaced by a transfusion of 6 units. This procedure seems unreasonable.

It is commonplace to insist that the hemoglobin concentration be "normal" before a patient comes to surgery. This is another instance where common sense appears to ignore physiology. It seems only common sense that the patient should have 14 gm. of hemoglobin. Actually, however, the hemoglobin concentration represents oxygen-carrying capacity, which is rarely a limiting factor during surgery. Blood dilution studies made on patients

(Continued on page A-46)



Tessalon perles stop cough fast—and they're convenient to take. No mess, no spillage, no awkward spoons or bottles to carry around. Another advantage: *no taste.* An exact, effective dose is sealed in a tiny gelatin sphere.

Reasons *why* Tessalon stops cough so effectively: it acts where cough begins—in the chest; it acts at the cough reflex center—in the medulla; it acts promptly—within 15 to 20 minutes, the effect lasting up to 8 hours. Tessalon is *not* a narcotic, yet has been reported 2½ times more effective than codeine in suppressing cough.[1]

SUPPLIED: Tessalon *Perles*, 100 mg. (yellow); bottles of 100. Tessalon *Pediatric Perles* (for children under 10), 50 mg. (red); bottles of 100. *Also available* (for use when oral administration of Tessalon is precluded): *Ampuls*, 1 ml. (5 mg.); cartons of 5.

1. Shane, S. J., Krzyski, T. E., and Copp, S. E.: Canad. M. A. J. 77:600 (Sept. 15) 1957.

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SERPASIL®
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for the anxious hypertensive with or without tachycardia

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during surgical operations have demonstrated that, when blood volume is maintained, the vital signs do not begin to show a deficiency of oxygen-carrying capacity until the hemoglobin concentration is less than 7 gm.

The dangers of blood transfusion, infection, hemosiderosis and transfusion reaction, are well known. Try as we may we can only reduce the incidence of the reactions. We cannot eliminate them, and patients will continue to be damaged as a result of blood transfusions. For example, it was a tragedy when a young woman died from a bottle of blood. How much more tragic it seemed when it was learned that her hematocrit had been 40 per cent when the transfusion was begun.

Thoughtless prescription of blood transfusion is playing Russian roulette with bottles of blood instead of a revolver. While the odds are in the physician's favor that nothing will go wrong, the patient takes the risk.

REFERENCE

1. CANTOR, P. D.: A legal look at blood transfusions. GP 16:82 (August) 1957.

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indications: hypo-ovarianism, menometrorrhagia, postmenopausal therapy. **dosage:** 1 or 2 tablets, two or three times a day, according to symptoms. **supplied:** bottles of 100 and 1000 tablets.

Samples and literature to physicians on request.

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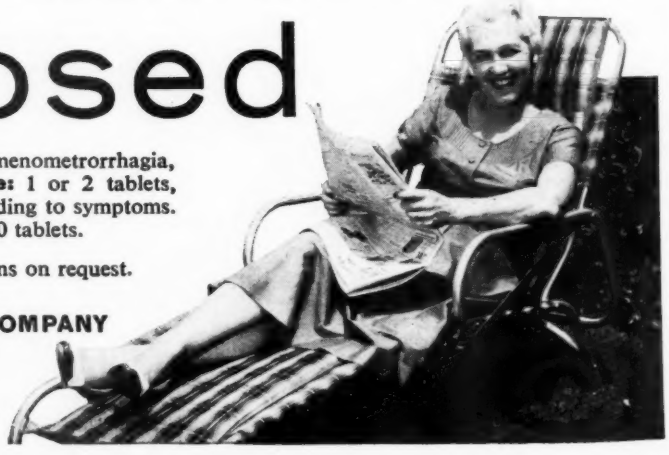

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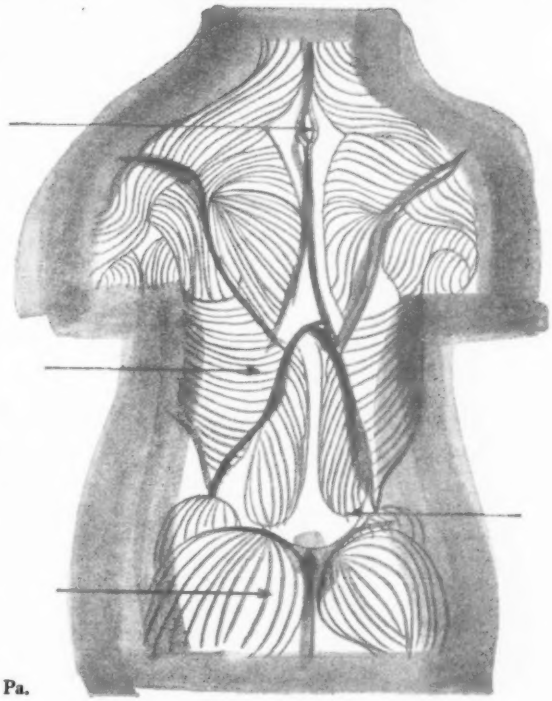

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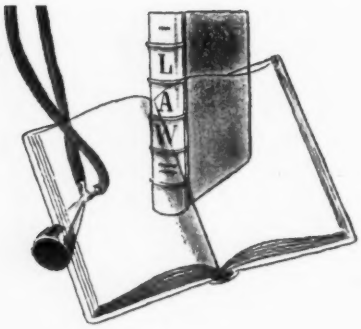

Forensic Medicine

Interpretation of Small Amounts of Carbon Monoxide in the Human Body

MILTON HELPERN*

New York University Post-Graduate Medical School, New York

THE suspicion and detection of the presence of small amounts of carbon monoxide in the blood are of considerable medicolegal as well as medical importance and significance. The astute physician, when he sees a patient with headache, nausea and vomiting, mental confusion and muscular incoordination, will consider the possibility that such symptoms are manifestations of carbon monoxide poisoning, but it is the rare physician who will correctly interpret and diagnose the basis for such findings.

MILTON HELPERN

When a person unknowingly is exposed to significant or dangerous amounts of carbon monoxide, the rapid disappearance of the transitory distressing symptoms and the spontaneous recovery which follow removal from the dangerous environment usually lead the victim or the physician to attribute the symptoms to some more common cause. Thus, many cases of mild carbon monoxide poisoning escape detection, and it is only subsequently when such a person returns to the dangerous environment, still unaware of the hazard, that more serious and even fatal poisoning may occur.

Among the fatalities reported several years ago at the second annual meeting of this Academy were a number of deaths from carbon monoxide due to prolonged inhalation of carbon monoxide-containing exhaust fumes from defective gas-flame refrigerators.[1] Several of the victims were ill prior to the fatal poisoning and sought medical attention, but the physicians consulted did not consider the inhalation of carbon monoxide as a cause of their symptoms. One woman complained of headache, nausea and vomiting. Her physician asked her what she had eaten prior to her illness, and finding she had ingested pork advised her not to eat it. The uneaten pork chops were found in the defective refrigerator when

(Continued on page A-54)

*Professor and Chairman, Department of Forensic Medicine, New York University Post-Graduate Medical School; Chief Medical Examiner, City of New York, New York.

Presented at the eleventh annual meeting of the American Academy of Forensic Sciences at Chicago.

PROTECTS AGAINST ANGINAL ATTACKS

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For convenience, write "CARTRAX 10" or "CARTRAX 20."

Supplied: **In bottles of 100.**

References: **1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.**

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friends found her dead, fatally poisoned by carbon monoxide.

Another report concerned two elderly persons living in a private home in which there was such a defective refrigerator. They were in the habit of keeping the windows closed in cool, damp weather. They complained to a friend who visited them that they felt sick, with headache and some nausea. The solicitous friend prepared ice bags with cubes from the defective refrigerator and then called a physician, but not sensing the urgency did not make it clear that an immediate visit was necessary. When the physician arrived next morning both victims were deeply unconscious, and they subsequently died from the delayed effects of carbon monoxide poisoning. Suspicion by the medical attendant that headache, nausea and vomiting might represent early symptoms of an increasing concentration of carbon monoxide in the blood and prompt removal of samples of blood for chemical examination would have established the true cause of the disability.

The concentration of carbon monoxide in blood, even in small quantity, does not change after the blood is removed and placed in a test tube or small bottle. Suspicion of carbon monoxide poisoning can save a person's life, and subsequent analysis of the blood by a qualified chemist establishes the diagnosis. In cases such as those just described, the presence of small amounts of carbon monoxide in the blood, even when severe incapacitation was absent, would indicate that poisoning was imminent and could be the basis for its prevention. The correct diagnosis of carbon monoxide poisoning in such cases of temporary disability can be substantiated only by the finding of some carbon monoxide in the blood. In the event of a legal action one can readily appreciate the value of such chemical corroboration of the clinical diagnosis of mild carbon monoxide poisoning.

In other instances a person may be discovered in a stuporous or comatose condition and taken to the hospital. Such persons may recover spontaneously, and recovery is more rapid if the diagnosis of carbon monoxide poisoning is correctly suspected and oxygen and carbon dioxide are given to hasten elimination of the carbon monoxide.

It is surprising in how many cases poisoning with carbon monoxide is correctly suspected and diagnosed and there is failure to analyze the blood. After a victim is removed from the atmosphere containing the carbon monoxide, it is eliminated fairly rapidly from his system. It is desirable to remove blood for chemical examination as soon as the diagnosis is suggested. If more than an hour elapses, the carbon monoxide content will be diminished considerably. If there is a moderate delay before a blood sample is taken, only small amounts of carbon monoxide will be found, but such amounts obviously have considerable corroborative significance in establishing the basis for unconsciousness or stupor. If several hours elapse, practically all the carbon monoxide will have been eliminated and there will be no chemical corroboration of the poisoning in the event the diagnosis is questioned.

Evaluation of the finding of small amounts of carbon monoxide in the blood therefore depends on circumstances. Without knowledge of the circumstances preceding the removal of the blood sample, accurate appraisal is not possible. In view of the fairly rapid elimination of carbon monoxide from the body, even a small amount in the blood may be significant and, in the absence of any exposure immediately before examination, would suggest a possible substantial and therefore dangerous exposure—perhaps an hour or two before the patient's visit, when the symptoms of headache, nausea and vomiting and other manifestations appeared. The recognition of what has happened to the patient may lead to lifesaving measures in eliminating the hazard. Failure to remove a blood sample for determination of the presence of carbon monoxide or delay in taking a blood sample may lead to an incorrect diagnosis and to persistence of the hazardous source of carbon monoxide with subsequent poisoning of the same person or of other persons. Therefore, from the standpoint of public health the accurate and prompt diagnosis of carbon monoxide poisoning, even nonfatal, is extremely important.

(Continued on page A-56)

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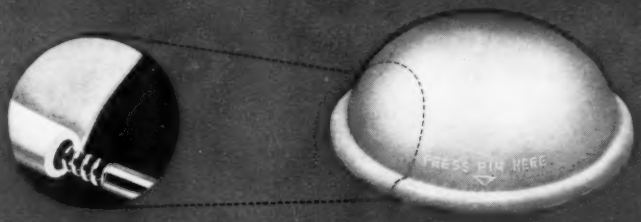

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Carbon Monoxide Poisoning Diagnosed as Meningitis

Several years ago a rather remarkable group of cases came to the attention of the Medical Examiner's Office in New York City. A young child was found dead in a small tenement flat, and six siblings and the mother were found unconscious. It was the impression of those who first came on the scene that the mother had given her children poison in an attempt to kill them. Her own unconsciousness was interpreted as the result of an overdose of sleeping pills, a box of pills being found beside her. The physician who first attended the victims, noting that the six unconscious children (ranging in age up to 12 years) were stiff and had rigid necks, made a diagnosis of meningitis, and the children were brought to the hospital by ambulance with that presumptive diagnosis. The unconscious mother was taken to another hospital by ambulance. A brief note on the chart suggested she had taken an overdose of sleeping pills, and a gastric lavage was prescribed.

One need only have had experience with similar cases of multiple unconscious victims and a dead victim to suspect immediately that carbon monoxide poisoning was the common cause. The medical examiner would not have been notified had there not been a dead child among the unconscious ones. He called the hospital where the children had been admitted to make a few tactful inquiries of the physician in charge. He spoke with the resident physician, who, when asked the diagnosis, said the six children had meningitis and spinal taps already had been completed on two of them. As tactfully as possible, it was suggested that carbon monoxide poisoning was a more likely cause of the unconsciousness, and this suggestion was received politely. It was also suggested that lumbar tap might not be necessary in the other four cases. When asked about the condition of the six children, the physician in charge stated that several already had regained consciousness. It was pointed out to him that six cases of meningitis in one family, with all six patients in coma at the same time, would be a most remarkable occurrence warranting immediate publication, for no such simultaneous occurrence of meningitis and coma in the same family had ever been described in medical literature.

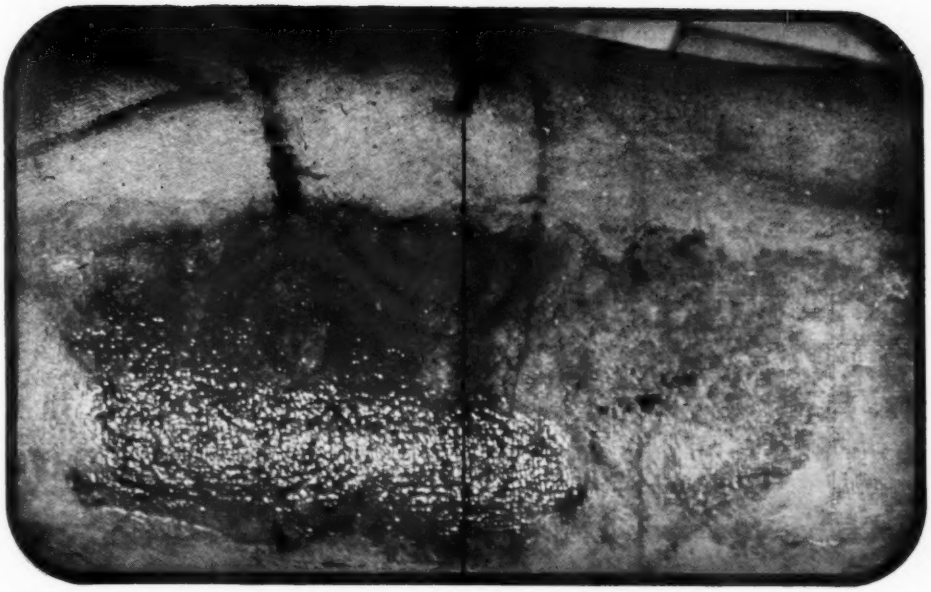
The physician was requested to remove samples of blood for carbon monoxide determination, but this was not done because of the urgency necessitated by the care of these patients. All of the six children recovered fairly promptly.

Inquiry then was made as to the condition of the mother, and again the suggested diagnosis of carbon monoxide poisoning was not accepted too enthusiastically by the physician in charge. The patient's stomach was washed out, a not altogether unhazardous procedure, especially when it was unnecessary. Again the request was made that blood be withdrawn for chemical examination to substantiate the diagnosis of carbon monoxide poisoning, but this was not done until many hours later; the laboratory reported that carbon monoxide was absent. The mother also gradually regained consciousness and recovered uneventfully.

Had it not been for the sad fact that one of the victims died, providing an opportunity to establish the correct diagnosis, I feel quite certain the surviving patients would never have been signed out as cases of carbon monoxide poisoning. I am quite confident that many similar cases go unrecognized and misdiagnosed. Autopsy on the body of the dead child disclosed what had been expected, namely, acute carbon monoxide poisoning, with a 50 per cent saturation of the blood with carbon monoxide. It is possible that this child also would have survived had there not been regurgitation and aspiration of gastric contents.

How did this series of poisoning from carbon monoxide occur? It happened during the winter in a cold-water flat without central heating. The mother, whose husband was in custody of the law, placed several large pots on the kitchen stove to provide hot water and to warm the kitchen and adjacent small rooms. With the windows closed and the flame impinging on the bottoms of the pots containing the boiling water, carbon monoxide was generated, even though the gas used for fuel was

(Continued on page A-58)



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Jeffords, J. V., and Hagerty, R. F.: Ann. Surg. *145*:169, 1957.

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of the natural type and did not contain any.

During the evening the mother had a gentleman caller. She told him that in the afternoon she had had a severe headache and had gone to a clinic where a diagnosis of sinusitis was made and an injection of penicillin was given. The headache had returned, and her friend graciously volunteered to go to the drugstore for some more penicillin. The druggist told him he could not buy penicillin without a prescription and suggested some headache pills instead. These were the pills found beside the mother when she was discovered unconscious.

The gentleman friend left later that night. The mother evidently put the children to bed and went to bed herself. The next morning the romantic friend returned. He rang the doorbell but there was no response. He thought he heard some snoring and moaning inside and went to get the superintendent. Together they broke in and found the mother and six children unconscious and one child dead. The range burners were lit and the heated pots were on the stove.

Carbon monoxide poisoning was not suspected, and, in fact, there was reluctance to accept the diagnosis even when it was proved. If one of the children had not died, it would have been very difficult to convince the owner of the building and others that the acute illness of all these persons was caused by carbon monoxide poisoning. Yet, even in the absence of a fatality, the prompt removal of a blood sample from any or all of the victims would have shown the presence of some carbon monoxide, significant even though it may have been in small quantity by the time the tests were made.

Carbon Monoxide as a Contributory Factor in Death From Other Causes

Occasionally a person is found dead in an atmosphere containing a dangerous amount of carbon monoxide and the death is not the result of inhalation of the gas or, at most, the carbon monoxide is a possible contributory factor in the death.

Several years ago, again during the time when there were fatalities from carbon monoxide poisoning associated with defective gas-flame refrigerators, the attention of the Medical Examiner's Office was called to the death of an elderly man in a small apartment where a gas-flame refrigerator was in use. The man returned home a short time before his wife, who worked as a domestic. Soon after she went into the kitchen she heard her husband fall to the floor. She went in immediately and was unable to revive him. Shortly thereafter he was pronounced dead.

Because of the attention being directed toward defective gas-flame refrigerators, the Health Department was notified immediately. Tests were made which revealed a concentration of carbon monoxide emanating from the flue and contained in the exhaust gases of approximately 0.1 per cent, or 1000 parts per million as tested with the Mine Safety Appliance Testing Device. The large and potentially dangerous amount of carbon monoxide in the atmosphere led to suspicion that it was a factor in the death. Nevertheless the death was sudden, almost instantaneous, and the lividity in the dependent portion of the body was not pink but blue. Subsequent autopsy disclosed a severe grade of occlusive coronary arteriosclerosis as the most reasonable explanation of the sudden death. The blood was tested for carbon monoxide, and only 8 per cent concentration was found. It was felt that this concentration of carbon monoxide was not lethal and could not with reasonable certainty or probability be considered a contributory factor in the death. Whether or not the carbon monoxide played a contributory role was speculative at most.

Subsequently this case came to litigation. The attorney representing the family was told of the medical examiner's findings and that the role of the carbon monoxide as a cause of death was extremely questionable in view of the suddenness of the death and its explanation by the substantial occlusive coronary artery disease, and the presence of only 8 per cent saturation of blood with carbon monoxide. It was extremely difficult to convince the attorney that the carbon monoxide was not a significant factor—even though the defective

(Continued on page A-60)

hen the distraction is intestinal . . .

on study of the man in the second row rightly adly speaks of diarrhea. And yet intestinal repose d be his lot with POLYMAGMA. For POLYMAGMA tains Claysorb, which is more than five times as ptive as kaolin. It enlists two antibiotics work- ynergistically. It permits a low-dose regimen with high effectiveness. And it has a taste and texture that wear well all through treatment.

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operation of the refrigerator with discharge of dangerous amounts of carbon monoxide was a potential hazard. The case was dismissed because there was no affirmative proof with reasonable certainty that carbon monoxide poisoning caused or contributed to the death.

Evaluation of the Amount of Carbon Monoxide in the Blood

Any evaluation of the finding of carbon monoxide in the blood at autopsy in regard to its role in the death must include not only the autopsy findings and the chemical examination of the blood for carbon monoxide but also a careful consideration of the circumstances surrounding or preceding the onset of the disability, the period of survival, the symptomatology and the manner of death. When persons are found dead in an atmosphere of the gas with concentrations of carbon monoxide in the blood above 50 per cent, regardless of other diseases or injuries carbon monoxide poisoning is indicated as the cause of death. Whether or not other significant conditions would be included in the cause of death would depend on what they were and their circumstances. When a victim is rescued after having been exposed to significant concentrations of carbon monoxide and is unconscious and subsequently dies, and the coma is not attributable to other causes as determined by autopsy and there is a survival period sufficiently long to provide for elimination of a substantial part or most of the carbon monoxide, then obviously the presence of a small amount of carbon monoxide and the absence of the usual finding of carboxyhemoglobin coloration of blood and organs are entirely consistent with the diagnosis of acute carbon monoxide poisoning as the cause of death.

There are cases in which death occurs about 24 hours after an acute poisoning without recovery of consciousness, with complete disappearance of carbon monoxide from the blood and without the usual suggestive anatomic changes in the central nervous system, heart, skin and elsewhere, and in these cases the diagnosis can be made only from a knowledge of the exposure and the prior circumstances. Any chemical test done on the blood within the first hours after exposure would show enough carbon monoxide, even though small in amount, to corroborate the correctness of the diagnosis.

Occasionally one encounters a case in which a person is exposed to a dangerous concentration of carbon monoxide, up to the point of unconsciousness, and then the atmospheric condition changes without the victim being moved. This may result in the disappearance of the carbon monoxide from the atmosphere and survival of the patient in coma for several hours in the carbon monoxide-free atmosphere. Any carbon monoxide present in the victim will be eliminated during this time, and death may occur without any carbon monoxide being present. One might be misled by such absence or by a small amount of carbon monoxide in the blood and fail to recognize that it actually is a delayed death from acute carbon monoxide poisoning.

In most delayed deaths there are suggestive anatomic changes resulting from the asphyxia and tissue anoxia to corroborate the impression that one is dealing with primary carbon monoxide poisoning. In most delayed deaths, and depending on whether the asphyxiation was brief or prolonged in the carbon monoxide-containing atmosphere (obviously only low concentrations, in the order of 1000 parts per million, can produce a slow, prolonged asphyxiation), one finds changes such as bullous eruptions of the skin, anoxic necrosis of the myocardium in the region of the papillary muscles, occasional bland mural thrombosis within the left ventricle, and commonly the classic symmetrical bilateral necrosis of the globus pallidus, the changes in the brain being accompanied by petechial and other types of small hemorrhages in the white matter, the latter hemorrhage more commonly seen in the slow types of acute asphyxiation.

Despite the impression among uninformed physicians, carbon monoxide, unlike lead or arsenic, is not a cumulative poison and is fairly rapidly eliminated from the body. Obviously it would be erroneous to attempt to relate a chronic degenerative disease of long duration to inhalation of carbon monoxide on the basis

(Continued on page A-62)

it started
as a
"cold"...
to prevent
the sequelae
of u.r.i. ...
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Sinusitis, otitis, tonsillitis, adenitis, bronchitis or pneumonitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection.(1) To protect and relieve the "cold" patient... ACHROCIDIN.
Usual dosage: 2 tablets or teaspoonfuls q.i.d. (equiv. 1 Gm. tetracycline). Each TABLET contains: ACHROMYCIN* Tetracycline HCl (125 mg.); phenacetin (120 mg.); caffeine (30 mg.); salicylamide (150 mg.); chlorothen citrate (25 mg.). Also as SYRUP, caffeine-free.
(1) Estimate based on epidemiologic study by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 71:122, Jan. 1933.
Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

of finding a small amount of carbon monoxide in the blood several years after the degenerative process manifested itself. Yet there are medicolegal cases in which such claim and proof were offered.

Summary

Failure to recognize the symptoms and signs of acute carbon monoxide poisoning may result in subsequent more serious or fatal exposure to the same unsuspected source of the gas.

Failure to corroborate a suspicion or definite diagnosis of carbon monoxide poisoning by prompt removal of a blood sample for chemical examination may lead to difficulty in establishing the diagnosis post mortem and legal proof in nonfatal and fatal cases in which there has been a period of survival long enough for the elimination of the gas in the blood.

REFERENCE

1. Trichter, J. B. and Helpern, M.: Accidental carbon monoxide poisoning due to domestic gas appliances and gas refrigerators. The problem in New York City and its control. Am. J. Pub. Health 42: 259 (March) 1952.

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MEETINGS and Postgraduate Courses

American College of Surgeons, San Francisco: 1960 Clinical Congress, October 27-November 1. For further information, write to: Dr. H. P. Saunders, 40 East Erie Street, Chicago 11.

International College of Angiology, Mexico City: First regional meeting, December 29-30, at the Hotel Continental. Scientific sessions will cover the areas of arterial occlusive disease and thrombo-embolic phenomena. For further information, write to: Mr. Joseph Tigani, Committee for Travel and Housing, 150 East 50th Street, New York.

Tulane University School of Medicine, New Orleans: Continuation courses for 1960:

General pediatrics, February 10-13
Surgery of the hand, March 3-5
Anesthesia, March 10-12
The early diagnosis and management of diseases of the ears, nose and throat in general practice, April 21-22

For further information, write to: Director, Division of Graduate Medicine, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans 12.

University of Colorado School of Medicine, Denver: Sixth annual general practice review, January 10-16, 1960. Discussions will be held on geriatric problems, medicine, pediatrics, surgery, trauma, obstetrics and gynecology, diabetes and atherosclerosis. For further information, write to: The Office of Postgraduate Medical Education, University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver 20.

University of Minnesota, Minneapolis: Courses for the general practitioner, to be given at the Center for Continuation Study, 1959 and 1960:

Orthopedics, November 16-18
Proctology, May 23-27
Cancer detection, all year

For further information, write to: Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.

Yale University School of Medicine, New Haven: Postgraduate courses:

Clinical epidemiology, weekly, beginning December 1
Ophthalmology, January 29, February 26, March 11, March 25
Pediatric psychiatry, February 15-April 4
Clinical psychiatry and psychology, January 27-April 20

For complete information on all postgraduate courses, write to: Dr. Arthur Ebbert, Jr., Assistant Dean of Postgraduate Medical Education, 333 Cedar Street, New Haven 11.

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Spondylolisthesis

PAUL C. HODGES*

THE term "spondylolisthesis," coined in 1853 by the German gynecologist Kilian,[1] designates a forward displacement of a lumbar vertebra, usually L5 on S1 (figures 1 and 2). Now that good-quality lateral films of the lumbosacral joint are commonplace, mild-grade spondylolisthesis is no longer rare, and it is found more frequently in men than in women.[2] Before the advent of x-ray, most of the recognized cases were in women, and were so severe that parturition was difficult or even impossible.

For some time the underlying cause of spondylolisthesis was controversial, which was not unusual, since the investigators had little to work with other than their wits and the findings palpated or observed clinically or during dissection in the operating room or the morgue. Rickets, tuberculosis, osteomalacia and numerous other conditions were suspected causes of spondylolisthesis. Lambl[3-5] was convinced that the principal causative factor was a condition he termed "hydrorhachis." This term has been translated for me as really meaning "meningocele with spinal defect" rather than "abnormal exudation of fluid into spinal canal," as given by Lang.[6]*

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Separate Neural Arch

As early as 1880, Neugebauer[7] concluded that a defect in the neural arch usually was present in spondylolisthesis, and he credited Lambl with prior recognition of this fact and with the introduction of the term "spondylolysis"† to designate it. In fact, Lambl had published a report on the examination of the pelvis of a Hottentot woman who had spondylolisthesis, in which he used the term "spondylolysis" and an illustration showing an arch defect (figure 3). We have it directly from Lambl[5] himself, however, that he did not mean to imply that arch defect was the primary

*My "school" German has been augmented by the generous and able assistance of my associate Dr. Klaus Ranniger, who was born and educated in Germany.

†This term and Neugebauer's term "spondyloschisis," in my opinion, should be abandoned in favor of "separate neural arch."

Pelvis normalis pulcherrima

FIGURE 1. Lithograph from Kilian's monograph,[1] showing normal female lumbosacral joint.

Pelvis paderbornensis

FIGURE 2. Lithograph of Paderborn pelvis from Kilian's monograph, showing grade 2 or 3 spondylolisthesis of L5 on S1. The usual osteophyte has formed at the sacral promontory, but has been broken off. The promontory itself has indented deeply into the inferior articular surface of L5.

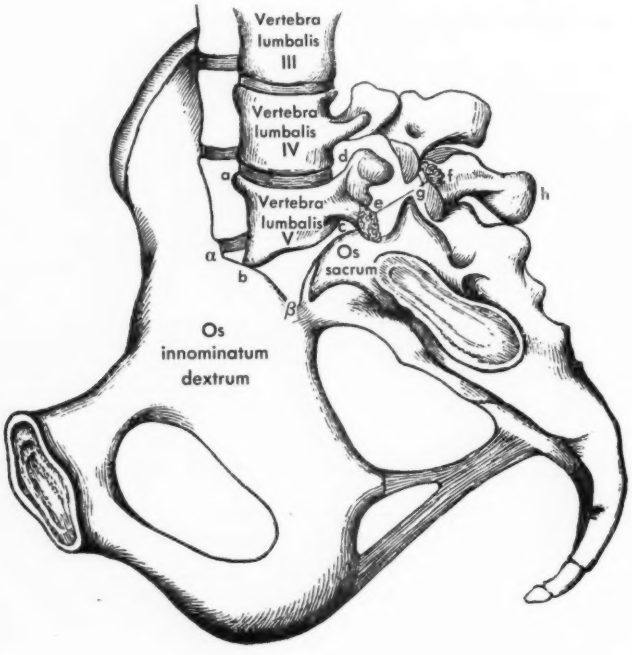


FIGURE 3. Woodcut from article by Lambl in which he introduced the term "spondylolysis." Neugebauer credited Lambl with understanding the significance of separate neural arch in spondylolisthesis, but probably Lambl misunderstood the situation, believing that the primary cause of spondylolisthesis was meningocele with associated congenital anomaly. At least in some cases and presumably in this one, he considered separation of the arch a secondary rather than a primary feature.

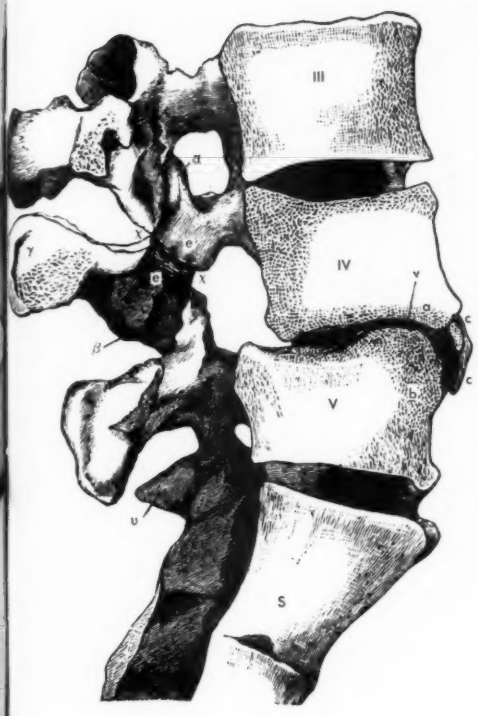


FIGURE 4. Neugebauer's woodcut[8] shows a specimen from Virchow's museum in which there is spondylolisthesis of L4 on 5 as a result of bilateral separate neural arch. The disk between L4 and 5 is narrowed and an osteophyte has formed at the anterior margin of the joint between L4 and 5.

causative factor in spondylolisthesis. Although his paper written in 1885 may confuse rather than clarify the etiology of spondylolisthesis, it is, at least, a fine example of polemics, including even a Biblical reference.

A woodcut of a spine reproduced in a monograph[8] written by Neugebauer in 1892 clearly shows an arch defect in L4 which has resulted in spondylolisthesis of L4 on 5 (figure 4). Neugebauer and many others have assumed that separate arches result from the congenital occurrence of anomalous extra centers which subsequently fail to fuse, but Batts[9] has shown the existence of such anomalous centers to be doubtful. Hitchcock[10] maintained that separate neural arches are arches in which the isthmus was fractured during delivery of the fetus and then was united only by fibrous tissue; however, Rowe and Röche[11] reported inability to produce such fractures experimentally. In one of the most extensive recent studies, Hilel,[12] in studying 19 cases of spondylolisthesis in 450 anatomic specimens, concluded that in most cases arch defect has been produced by a shearing action between the inferior articular facets of the segment above and the superior facets of the segment below the involved segment. He believes that the condition is not a fracture, but is a gradual resorption of bone along the line of repeated subminimal injuries, with narrowing of an intervertebral disk possibly playing a role.

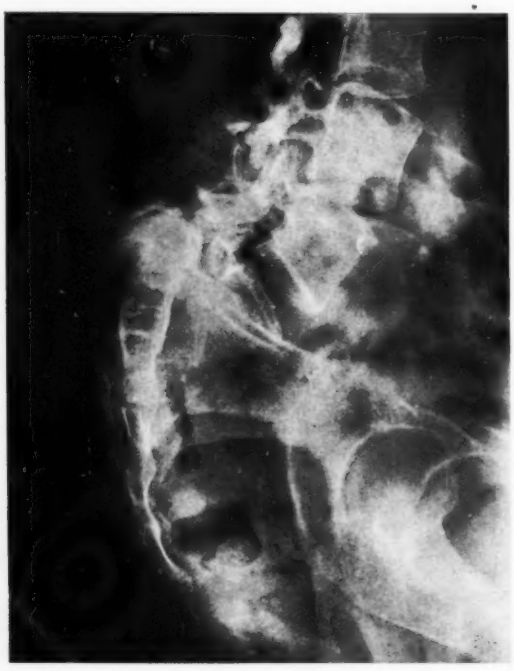
Spondylolisthesis Without Separate Neural Arch

Kilian's coined term "spondylolisthesis" means "a slipping down of the spine," and it is well not to use the term for the displacement caused by fracture-dislocation. Almost invariably the underlying factor is separate neural arch. Occasionally, however, chronic degenerative arthritis may erode adjacent facets sufficiently to allow mild-grade spondylolisthesis (figure 5).

X-ray Diagnosis

The first requisite of x-ray diagnosis is a fine-quality lateral lumbosacral spine film, and this is best made with a moving Potter grid of high ratio, at least 12 to 1 and preferably 16 to 1. The patient must be positioned and immobilized with great care; target-film distance should be as great as the design of the grid permits, and a collimator should be used to restrict the incident beam to the smallest size consistent with the size of the film being used. It is well to work with rather high voltage and a thick filter to reduce the tissue dose, and it is desirable to use a large enough milliampere second setting so that the exposure will be brief, thus minimizing the likelihood of the patient's moving during exposure of the film. When the film is of good quality, the diagnosis of spondylolisthesis is usually obvious. The displacement of the lumbar segments anteriorly relative to those below can be discerned most easily by examining the line formed by the posterior bodies of the

FIGURE 5. Grade 1 spondylolisthesis of L4 on 5, which was caused by degenerative arthritic erosion of the inferior articular facet of L4 and the superior facet of L5. The patient, a 48 year old woman, had back pain and muscle wasting.



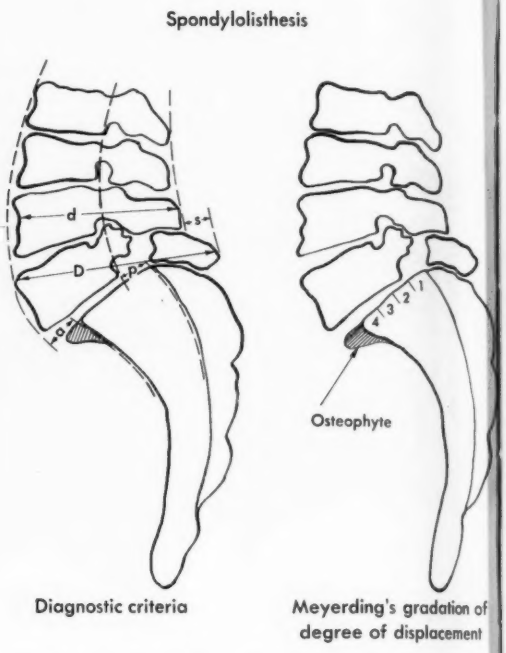


FIGURE 6. Redrawn from Meyerding to illustrate his method of grading the degree of spondylolisthesis. Shown are the break in the alignment of the posterior surfaces of the lumbar and sacral segments at the level of the spondylolisthesis, apparent lack of offset in the outline of the anterior surfaces of the lumbar and sacral segments because of the osteophyte on the sacral promontory, and increased distance from anterior surface of body of involved segment to the tip of its spinous process.

FIGURE 7. Grade 5 spondylolisthesis of L5 on S1. The body of L5 has descended into the pelvis to the level of S3. Achilles tendon reflexes were absent bilaterally in this 43 year old woman who had a 15 month history of rectal and vaginal paresthesia, aggravated by standing or walking.

lumbar and sacral vertebrae. Normally, this line is an unbroken curve, but in spondylolisthesis it is broken sharply at the site of the lesion. Study of the anterior border of the bodies of lumbar and sacral segments is less rewarding, because if spondylolisthesis has been present for some time an osteophyte will have formed on the sacrum at the promontory, which, at least to the inexperienced eye, looks like the promontory itself (figures 6 to 8).

Occasionally, posterior oblique films will

FIGURE 8. Grade 1 spondylolisthesis of L4 on 5. Left lateral view shows the slight anterior displacement, and suggests but does not absolutely establish the existence of the arch defect which certainly must be present.

The patient, a 40 year old man, had acute back pain following strain, but it seems probable that, except for the fact that the pain instigated an x-ray examination of the spine, no relationship existed between the symptoms and the spondylolisthesis. There was complete remission of symptoms after two weeks of bed rest, and the patient has resumed full duty.

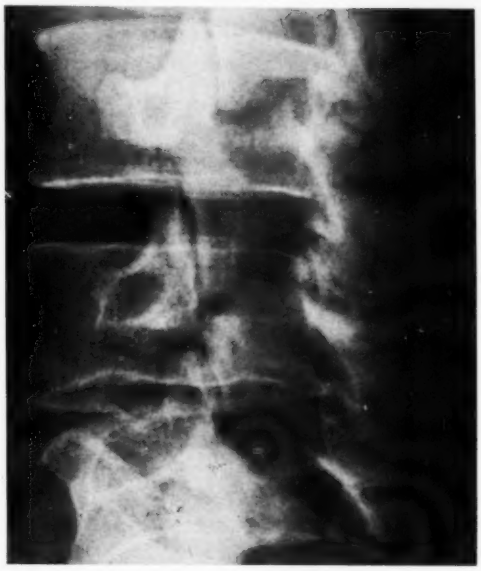


FIGURE 9. Same case as figure 8, right posterior oblique view. In the upper third of the illustration may be seen the normal third lumbar vertebra, with its normal superior and inferior articular facets making up a pattern that has been described as resembling the snout, ears, eye, shoulders and front legs of a Scottish terrier.

However, in the fourth lumbar vertebra, seen in the center of the illustration, a defect in the arch shows as a black stripe, which has been likened to the collar on the "dog."

FIGURE 10. Same case as figure 8, left posterior oblique view. The defect on the left side, which shows even more clearly than the one on the right, does, indeed, look like a collar about the neck of the "dog."

Figures 8, 9 and 10, courtesy of Drs. Roger Lough and Raymond J. Pellicore, Illinois Central Hospital, Chicago, Illinois.

show the defect directly (figures 9 and 10), but it is only occasionally that one is fortunate enough to see the defect well even if it is present. The patient lies on his back, rotates 45 degrees to the right, and, with the right articular facets centered with the film

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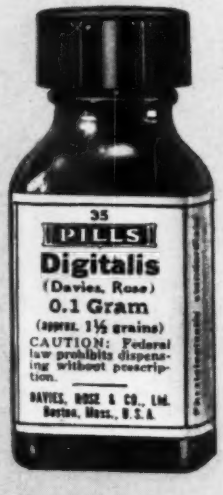

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center and with the beam of radiation, a film is made. The patient is then turned to a left posterior 45 degree oblique position and the left articular facets are examined. If the patient has been well positioned, the normal articular facets bear a fancied likeness to the front legs, shoulders, snout, eye and ears of a Scottish terrier, and, if a defect is present in the arch, it shows as a dark stripe simulating the appearance of a black leather collar on the neck of the "dog."

Treatment

Frequently in spondylolisthesis, there are no symptoms at all, and the condition is found accidentally during x-ray examinations of the lower abdominal or pelvic region for some other condition. When there is stubborn pain that does not disappear with a week or so of bed rest, it may be desirable to fuse the affected joint to stabilize it. It is quite impossible to "reduce" a spondylolisthesis, and one should never attempt to do so by appliances or surgery.

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Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA

Coarctation of the aorta—Dr. C. J. Officer Brown and co-workers have published the results of treating a series of 100 patients with coarctation of the aorta. Symptoms in these patients included pain in the legs and chest, headaches, and dyspnea on exertion. Nine patients had symptoms of some serious complication; 41 were asymptomatic. In most patients the systolic and diastolic blood pressure was elevated in both arms. In the two patients in whom the pressure in the right arm was markedly lowered, the coarctation was above the subclavian artery. Associated anomalies included aortic incompetence in 17 patients, aortic stenosis in eight patients, and patent ductus arteriosus in four patients. Three patients had a ventricular septal defect.

Roentgenographic findings were described under three headings: appearance of the upper part of the mediastinum; size and shape of the heart; and rib notching, which was present in all patients. The characteristic features of coarctation of the aorta are found in that portion of the cardio-aortic outline formed by the aorta. Proximal to the coarctation, the aorta is frequently elongated and slender, and the left subclavian artery is enlarged at its point of origin; a varying degree of narrowing is present at the coarctation, and so-called poststenotic dilatation of the aorta often occurs immediately distal to the coarctation. In addition, the stenosis may pull the descending part of the arch downward and inward. The relative severity of these various abnormalities determines whether or not the deformity of the normal outline of the upper part of the mediastinum can be seen by roentgenographic examination.

In view of the serious prognosis, the authors believe that corrective surgical procedures should be done in all patients except those who have extremely mild forms of the condition. In this series, surgery was performed in 74 of the 100 patients, with an operative mortality of 7 per cent. Hypotension induced with Arfonad was found to be a valuable adjunct to the operation. Interrupted sutures using No. 00000 arterial silk were used for the anastomoses.

Follow-up results showed that the blood pressure was normal before surgery in six of the 67 patients operated on successfully. In 48 patients the blood pressure in the upper limbs was reduced to below 140/90, with a corresponding rise in the pressure in the femoral artery. Two of these patients died from unrelieved aortic stenosis. In 11 patients, the blood pressure was lowered, but not to normal limits. Five of these patients had aortic regurgitation in addition to coarctation, and one required a graft. Two other patients had had a subclavian aortic anastomosis;

(Continued on page A-111)

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Control of Habitual Abortion

Disturbed capillary permeability and lowered capillary resistance, as well as the tendency toward edema and fluid retention, are well recognized in pregnancy (1, 2, 3, 4). The bioflavonoids have been shown effective in controlling the susceptibility to edema in pregnancy (5) and their routine prenatal use has been suggested (6).

Ecchymotic areas resulting from bruises and positive capillary fragility tests have frequently been observed in habitual aborters (7). Patients having a history of two or more spontaneous abortions have shown a marked improvement in fetal salvage after the addition of *Hesperidin* (a citrus bioflavonoid), ascorbic acid and other factors to the therapeutic regimen (8, 9, 12, 14, 15, 16). Other investigators have reported extensive use of the citrus bioflavonoids in the management of pregnancy with excellent results (18, 19, 20).

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The rationale of *Hesperidin* and other citrus bioflavonoids—in conjunction with vitamin C, nutritional factors or other therapeutic agents—as adjuncts in the management of pregnancy and its complications, spontaneous abortion and erythroblastosis fetalis, is based on the premise and observation that capillary involvement may be a contributing factor.

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in one the blood pressure was reduced from 215/80 to 155/100, and in the other it was reduced from 215/115 to 170/100. One of two patients in whom the blood pressure was not reduced had aortic incompetence in addition to the coarctation.

Congenital talipes equinovarus—In a discussion of a rational treatment for congenital talipes equinovarus, Dr. J. E. Critchley described the technics used by Dr. Hiram Kite of Atlanta. Dr. Critchley had earlier visited Dr. Kite's hospital, which is a major American center for treatment of this condition.

The variations in the methods of treating clubfoot indicate that unsatisfactory results and failures have occurred in many cases. The use of force undoubtedly has been a principal cause of failures. Correction by forcible manipulation results not in stretching but in tearing of soft tissues and even bone.

Dr. Kite's method of treatment is essentially gentle correction of the deformity and maintenance of position by plaster of paris. Gentle manipulation is the only method which seems to be always successful, irrespective of the child's age. The importance of correcting the adduction and inversion before correcting the talipes equinus cannot be overemphasized. If this is done, the talipes equinus can be corrected more easily, and "boating" of the foot is avoided.

The reports abstracted here appeared in the *Medical Journal of Australia.*

AUSTRIA

Plasmocytoma—At a meeting of the Society of Viennese Physicians, G. Salem and R. Wenger reported the case of a 69 year old woman whose left thigh bone broke spontaneously more than five years ago. Microscopic examination of tissue removed from the bone indicated a plasmocytoma. Following operation, the woman has been free of complaints, and examinations have shown that the local process has not become generalized. Drs. Salem and Wenger discussed the concept and problems of solitary myeloma, pointing out the necessity of appropriate follow-up studies of patients with this condition.

(Continued on page A-112)

Urogenital tuberculosis—B. Bibus presented a lecture on the problems of urogenital tuberculosis at the same meeting. Although modern therapeutic methods have greatly reduced mortality from tuberculosis, the number of incomplete cures, which leave a patient permanently disabled, has not abated. Such cures are increasing, and many more people with tuberculosis reach the late, progressive stage of the disease. This is especially true of patients with urogenital tuberculosis, for tuberculous kidneys must be removed in 50 per cent of such patients, resulting in incomplete cure.

Procedures and practices which would lead to improved results and avoidance of serious disabilities in cases of urogenital tuberculosis were discussed. Surgical therapy was stressed, and sociomedical measures were suggested. These measures include periodic urinalysis for all patients having or suspected of having tuberculosis; follow-up care by urologists; and the establishment of special departments at sanatoriums where patients with urogenital tuberculosis would receive permanent urologic care. Although other countries have instituted these practices, Austria has not yet established such procedures.

Malignancy following ovarian endometriosis—A case of malignant degeneration of ovarian endometrial cysts was discussed by Dr. E. Kofler at a meeting of the Austrian Society for Gynecology and Obstetrics. A 46 year old woman with bilateral ovarian tumors underwent a complete hysterectomy, including removal of the adnexa. Histologic examination of the surgical specimen showed that typical chocolate cysts were present in both ovaries; in addition, the endometrial cyst on the left side was found to contain a polypous malignant adenoma which was the size of a cherry.

Eighteen months later, after an interval during which she had no symptoms, the patient was readmitted to hospital. Her general condition was markedly worse, and an immobile hard tumor as large as a child's head was present in the true pelvis. Clinical findings showed a massive recurrence of the malignancy.

Only about 30 cases of malignant degeneration of endometrial cysts in the ovary have been reported in the literature; in some of these cases there was inadequate evidence of malignancy. However, Dr. Kofler believes that even though such cases are rare surgical intervention should be carried out immediately when endometriosis is suspected. At present, surgical treatment appears to be more successful than does conservative therapy for endometriosis.

BRAZIL

Infertility—Afrânio de Alencar Matos has defined infertility as the incapacity of woman to carry out the normal process of conception. The negative psychologic repercussions caused by the repeated emotional trauma associated with this condition, the consequent conjugal disturbances, its world-wide prevalence, and the complexity of causal factors that require extensive medical studies have contributed to the medical and social significance of infertility.

Dr. Matos pointed out that many efforts to treat infertility have been successful and that progress in treatment is being made, contrary to the widespread pessimism. The variety and extent of factors causing infertility require a systematic and complete medical investigation which can be made only by a specialist. Abortion was cited as the chief cause of infertility. Dr. Matos recommended that due to the prevalence and severity of this problem public health authorities should provide special services for dealing with infertility in hospitals having adequate facilities.

Radiopelvimetry according to the Colcher-Sussman technic—In an article in the *Revista de gynecologia e d'obstetricia*, Geraldo V. de Azevedo briefly outlined the history of methods of radiopelvimetry and described the technic of Colcher and Sussman. While this method requires only two x-rays, it permits sufficiently accurate measurement of the anteroposterior and transverse diameters of the inlet, excavation and outlet of the pelvis and the head of the fetus; this is accomplished by measuring the subpubic angle. In cases of breech presentation, the author recommended cephalometry performed according to the technic of Rogers, Jr. and Griffin.

After outlining the advantages of the Colcher-Sussman method, Dr. de Azevedo stated that radiopelvimetry is indicated in all first births as well as in subsequent births in which the mother previously has had dystocia or a cesarean section.

Ovarian pregnancy—After reviewing the lit-

(Continued on page A-114)

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erature on ovarian pregnancy, Albérico Câmara concluded that this condition is extremely rare. He reported in the *Revista de gynecologia e d'obstetricia* that he believes that ovarian pregnancy can be diagnosed at surgery only. The standards still used today for classifying a pregnancy as ovarian are those which were proposed by Spiegelberg in 1878.

ENGLAND

Biologic aspects of aging—At the annual meeting of the British Medical Association, held in conjunction with the Canadian Medical Association at Edinburgh, there were a number of plenary sessions on general topics and round-table conferences on specially selected topics. One of the most interesting was on the problems of an aging population.

Opening the discussion on aging, Professor P. L. Krohn, Birmingham, said that none of the theories purporting to account for the gradual loss of vitality and the increasing likelihood of death as we become older is generally acceptable. Proficiency in particular tests rises to peaks at different ages; thereafter, there are different rates of decline, which suggest that the individual systems of the body age at very different rates. The life span of rodents can be increased by restricting caloric intake; therefore, the control of nutrition and, in particular, the control of obesity might play an important part in increasing the life span. A diet giving the maximal rate of growth is not associated with long life.

Dr. J. H. Sheldon, Wolverhampton, said that although aging presents society with problems it is less than fair to regard age as a problem, for the old make notable contributions to our social integrity. Until the early 70s, at least, they are donors rather than debtors. It is the proportion of old people which matters to society. Although within the next 20 years there will be an increase in the number of old people in Great Britain, the resultant problems might not be as severe as are feared, due to the improvement in birth rates since the war. While it takes 65 years "to grow" an old man, it takes only 20 years to make someone old enough to look after him.

(Continued on page A-116)

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The declared policy in Great Britain is to help elderly people to live in their own homes as long as possible. The vast majority can look after themselves until age 75; after that age, the capacity to lead an independent life becomes precarious. As Dr. Sheldon sees it, the major problem is to promote and continue those features in the structure of our society which will allow human ties to continue for the comfort and care of the elderly.

Standards of growth in children—According to a report by the Ministry of Health entitled "Standards of normal weight in infancy," the average birth weight of boys is 7.53 lb., and that of girls is 7.21 lb. These figures are based on a survey of 17,308 children in 11 localities in England and Wales. The birth weight of first-born children is lower than that of later-born children. It also was noted that the birth weight of girls and probably of boys is lower in the unskilled classes than in the professional and managerial groups. Although these individual differences are small, the cumulative total represents quite big differences in birth weights considered according to social class and order of birth. About 7 per cent of first-born boys of unskilled parents weigh 9 lb. or more at birth; the corresponding figure for later-born babies of parents in the professional and managerial classes is 20 per cent or more.

From birth to the age of three years, four phases of growth can be distinguished: (1) relatively variable growth for the first four weeks; (2) a rapid increase to age 16 weeks; (3) a gradual and slight increase in the rate of growth up to 16 months; and (4) a fairly uniform growth rate until the child reaches three years of age, when, on the average, boys weigh about 32.5 lb. and girls weigh about 31.5 lb.

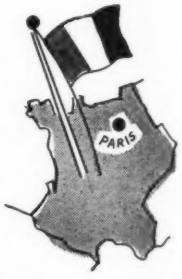
Respiratory symptoms and the diagnosis of chronic bronchitis—The mortality from bronchitis in England and Wales is four times greater in middle-aged men (40 to 59 years) than in middle-aged women, according to Dr. C. M. Fletcher, London Postgraduate Medical School, and his associates Drs. P. C. Elmes, A. S. Fairbairn and C. H. Wood, who recently published a careful study of this problem in the *British Medical Journal*. The picture of bronchitis that emerges from this study is different for the two sexes. Cough and sputum, but no other symptoms, were more prevalent in men; all symptoms showed an age gradient in men but not in women. A significant depression of ventilative capacity in association with the symptoms occurred only in men.

A study was made of 192 postmen and 192 women employed by the post office in London. The subjects, aged 40 to 59 years, were questioned as to symptoms; measurements were made of sputum volume and of ventilative capacity, and sick leave records were inspected. The men had more cough and sputum than did the women, but the prevalence of other symptoms and of chest illnesses was similar in the two sexes. Symptoms increased with age in the men but not in the women.

Differences in smoking habits do not account entirely for the variation in the prevalence of cough and sputum or for the lack of age gradient in women. It is possible that women with a disability are less likely to continue working than are men; thus, occupational selection may be partly responsible. However, disability would be less likely to interfere with the sedentary work of the women than with that of the men.

Exposure of the men to the polluted air of the City of London may partially account for the differences observed between the sexes in regard to bronchitis, for postmen exposed to air pollution in their daily rounds have a higher rate of sick leave due to this disease than do civil servants working indoors; this difference increases with advancing age. However, the striking lack of impairment of ventilative function in association with cough and sputum and recurrent chest illnesses in women does suggest that bronchial hypersecretion and recurrent infection have different consequences in the two sexes. This factor may be at least partly responsible for the variation between the sexes regarding disability and mortality from chronic bronchitis.

FRANCE



Medically treated peptic ulcer—Statistics on 104 patients who had received medical treatment for gastric or duodenal ulcer, or both, for several years were reported by Dr. Milliez in the *Bulletin de la Société des hôpitaux de Paris*. He compared the results of his study with other French statistics on several hundred peptic

(Continued on page A-118)

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ulcer patients. The report illustrates interesting differences of opinion between French and American doctors.

The treatment for peptic ulcer described by the author extends over a 50 day period, and consists of about 30 intravenous injections of proteins (casein proteinate or pancreatic peptone, with or without atropine bromide). At the same time, a ferro-ferric sodium preparation is given intramuscularly, and bismuth subnitrate and sedatives are given orally. The diet is liberal, but without spices, alcohol or acids. The patient is ordered to discontinue his usual business routine, and those with severe ulcers are put to bed. Next, Dr. Milliez institutes a prolonged maintenance treatment: histidine injections and ascorbic acid for 10 days, then bismuth orally for 10 days, and finally bromides and barbiturates for 10 days. If necessary, this treatment is supplemented with atropine, injections of placental extracts, and occasionally, when the inflammation is persistent, injections of ferro-ferric sodium.

In the author's opinion, this maintenance therapy must be continued by patients with gastric ulcer for several months, and by those with duodenal ulcer for four years. Since it is hard to provide regular care over a long period for sick persons who no longer feel sick, two-thirds of the patients did not follow the treatment long enough.

The initial treatment was successful in 75 per cent of the patients with duodenal ulcers, but the main problem was to avert new attacks. Success in doing so proved to be related to the number of years of treatment. In reviewing the histories of patients who had been followed for four to nine years, it was found that the rate of relapse among those who had discontinued the treatment after one year was 75 per cent, after two years 60 per cent, after three years 25 per cent, and after four years 20 per cent. Twenty-two per cent of the patients required surgical intervention.

Medical treatment in patients with gastric ulcer was not so successful; one-half of the patients were eventually operated on. The duration of maintenance therapy did not exceed eight months. Although the risk of relapse was less than that in duodenal ulcer, it was not reduced by prolonged therapy.

These statistics are generally in agreement with other French medical statistics which formerly grouped ulcer patients under "good results," "not operated on," or "failures in need of operation." All are in agreement that the patient's age does not influence the course of the disease.

Vegetable fats and atherosclerosis—In *La Presse médicale*, Professor de Gennes reported his opinions and findings regarding diets rich in vegetable lipids for treatment of atherosclerosis.

Taking into account the results obtained with placebo drugs, and the influence of mental factors on the level of the blood cholesterol, Professor de Gennes is not certain of the effectiveness of unsaturated vegetable fatty acids in treating atherosclerosis.

He conducted wholesale experiments on two groups of rats. One group was fed on butter and the other on oil; 80 per cent of the caloric intake was in the form of lipids. Some subgroups of the animals were given vitamin complexes. The high levels of blood cholesterol resulting from a disturbance of the lipid metabolism were similar in both groups. Pyridoxine and methionine lessened the metabolic imbalance.

The author believes that a diet loaded with vegetable oils lacks the vitamins essential to the utilization of such lipids. However, these vitamins are present in butter. Therefore, he believes that we should question a dietetic overload of vegetable lipids and its share in the causation of atherosclerosis and hypercholesteremia.

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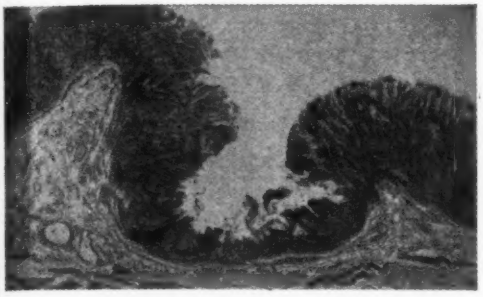
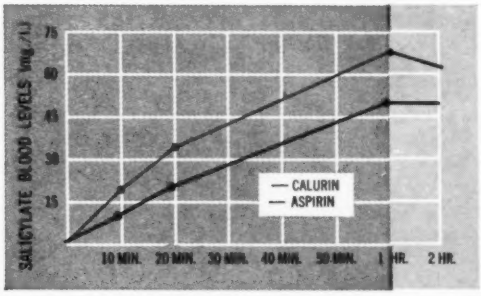


Particle-induced ulceration — section through lesion found in gastrectomy specimen. An aspirin particle was found firmly imbedded in this undermined erosion. Such lesions may be associated with the relative insolubility of aspirin, which remains in particulate form after dispersion in gastric contents.



Calurin, being freely soluble, is promptly available for absorption into the systemic circulation. Salicylate blood levels in 12 subjects receiving both Calurin and plain aspirin were found to rise more than twice as high within ten minutes following Calurin. Also, these levels persisted higher for at least two hours.[11]

CALURIN is the aspirin of choice, especially when high-dosage, long-term therapy is indicated:

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Dosage: Each tablet of Calurin is equivalent to 300 mg. (5 gr.) of acetylsalicylic acid. For relief of pain and fever in adult patients, the usual dose of Calurin is 1 to 3 tablets every 4 hours, as needed; in arthritic states, 2 or 3 tablets 3 or 4 times daily; in rheumatic fever, 3 to 5 tablets 4 or 5 times daily. For children over 6 years, the usual dose is 1 tablet every 4 hours; for children 3 to 6 years, ½ tablet every 4 hours, as required. Not recommended for children under 3.

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*TRADEMARK

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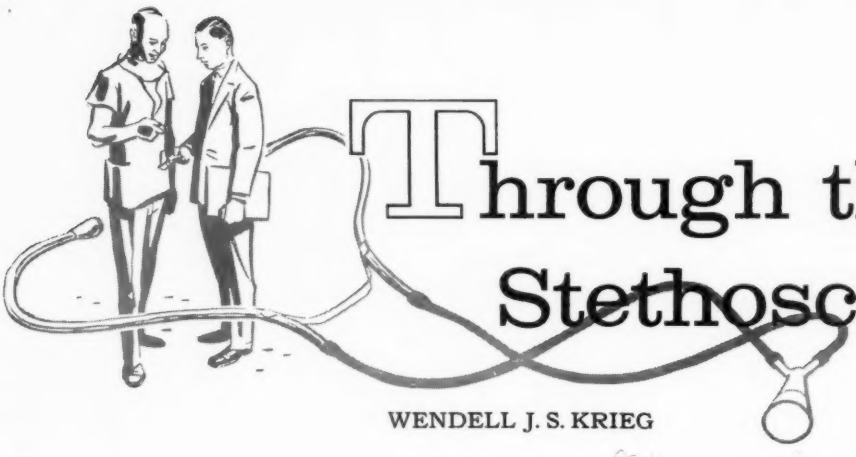

Through the Stethoscope

WENDELL J. S. KRIEG

My dear son:

In this letter I want to comment about your colleagues, the persons with whom you will have to work. Although the world may regard the professor as a type, you and I know that a faculty is a collection of individuals of varied types, but within a range. With only rare exceptions, they are courteous, honorable, responsible, industrious, undemonstrative, stubborn, patient, kindly; but they are not likely to be cordial, sociable, generous or sentimental. They will blanch at a wrong case ending in their own language, but will be content to be sublimely ignorant of yours.

They will resign for being passed over in an appointment, but will quietly endure unnecessary impecuniousness for years. They will take the same train home through all seasons for years, and never once think to look at the sunset. A particularly cozy cocktail lounge in the next block will be completely unknown to them. Every day they will carry a sandwich and make coffee in a beaker, thus missing the opportunity to be a member of a brilliant luncheon club that a merchant would pay well to attend. I have always felt that one of the irreplaceable advantages of academic life is the opportunity to associate daily with men, each of whom is learned in a different subject, many of whom have traveled widely and have had, in one way or another, distinguished careers, and who know interesting people. In the metropolitan universities this opportunity is badly muffed. Except for a few cronies, the professor is likely to be a lonely man. This does not seem to be due to any gaucherie or unsophistication; rather, it seems a direct result of his individualism and of living according to principle. What an opportunity a professorship is for developing an interesting and brilliant social life! I know that there is a stronger tug from his studies, and that the peace, security and satisfaction that the pursuit of them brings is greater than the urge to sociability. I know that social life exists largely to fill a void and to escape boredom, and that it is created largely by the ladies. Yet there is much in the life that can be shared, and mutually similar viewpoints can be reinforced. So, I wish you would emphasize the social aspects of your life, even to the apparent detriment of your work.

I fear that the worst light in which science as a career can be shown is in the repression of the emotions that are naturally a part of it. Persons who by nature do not enjoy emotional stimulation or expression are, perhaps, more inclined to take up science in the first place (and certainly there should be a niche for them), but when in other groups I often compare. Musicians, advertising executives and artists value alertness, cleverness and originality, for they know that their success depends on these traits. A luncheon with such a group

(Continued on page A-126)

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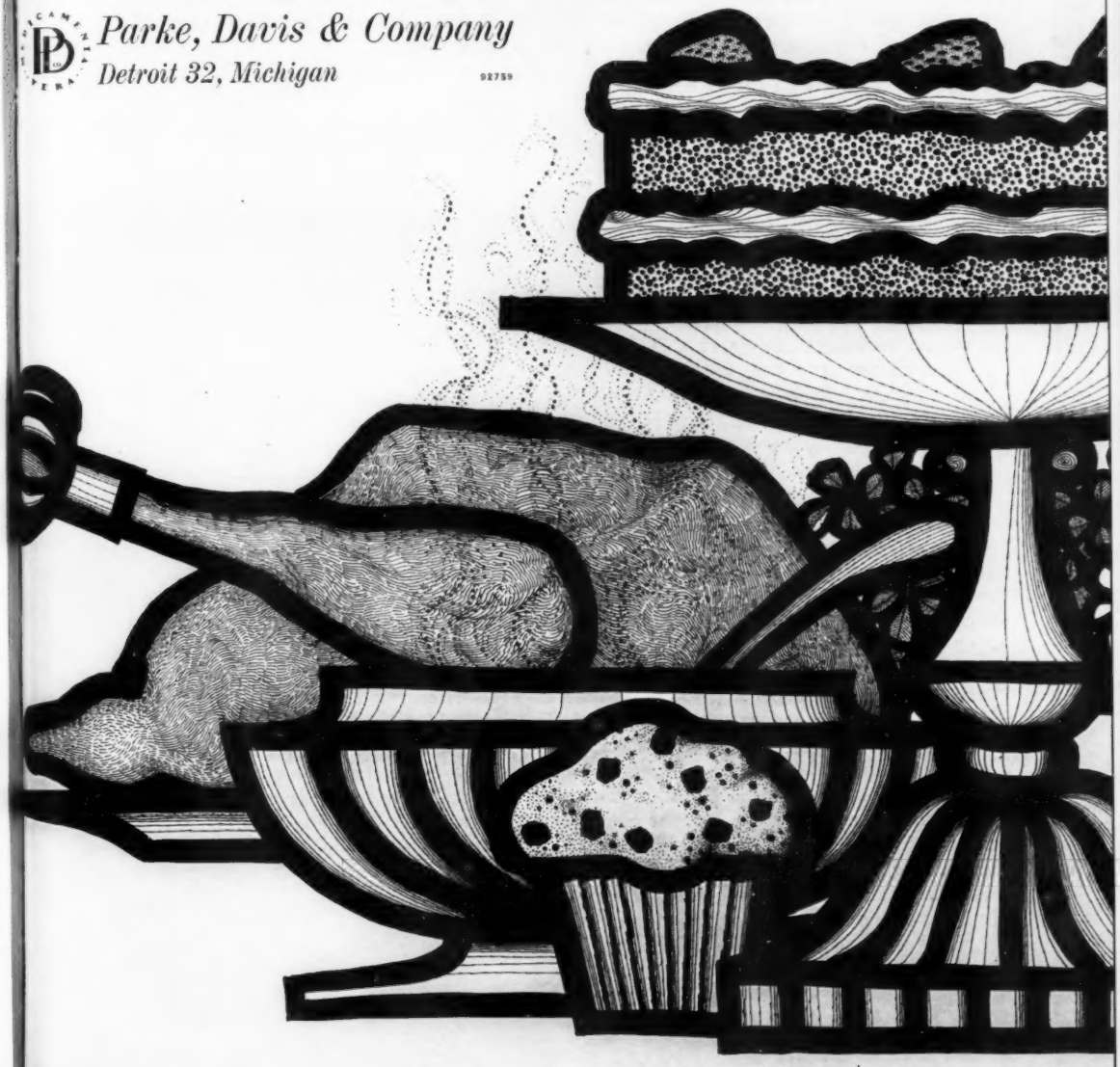


is likely to be more interesting than one with men who weigh every word and keep the proper academic deliberation.

A friend whom I see once a year at meetings asks me what I am doing, and I tell him of my recent investigations. As he listens, his lower lip curls more and more, and finally he says, "I know, but are you having any fun?"

There are various kinds of mental approaches among persons who have elected the scientific career. There is the plodder, a well-recognized type that needs no comment and that is recalled to mind when the professor is mentioned. A less clear-cut type is one I call the undeviating. Persons of this type are enviable. They perform their work with concentration. They do not look up when you walk by, and spring weather doesn't bother them. They tread effortlessly the path of rectitude. At conventions they talk soberly, have one beer, and are in bed by 11 P.M. If given a committee job, they will do it well and will make a sensible report. They don't notice a passing lady who has made your knees weaken. They patiently work out the values necessary to plot a curve, but they may not see that the curve is really a strophoid.

A third, more rare type is the chap, interested in everything, who can't help noticing an unusual automobile license plate or unusual circumstances in an experiment. He is curious about everything that he doesn't know, and may keep several irons in the fire. He may have trouble finishing any one task, but his receptivity may open the way to a new combination of observations that result in a correct interpretation.

When you have published your doctorate thesis, you will be eligible to join the national society of your subject. You will have to be recommended for this, and your sponsor may forget. Remind him well ahead of time, as you may be at another institution the next year, and it is important to be independent in the matter of scientific reports as soon as possible. The same holds true for routine "honors," such as Sigma Xi. To have those you merit at an early stage of your career keeps your *curriculum vitae* from looking too blank in your callow years. However, it is improper to ask for membership in the more recherché societies or clubs that are open only by invitation. I don't think it is well to join specialty societies in fields outside your own in which you do not intend to participate. Accumulating honorary societies is one thing; accumulating working societies is quite another.

Once you have been accepted in your national society, try to attend its meeting each year and to present a paper. You will gradually become known to your colleagues, and will be in a position to be observed for a possible call. More important, you will come to know the group whose interests are closest to yours and who represent your subject in other schools. Next to your own family, these are the most important people in the world to you. You will see them annually for as long as 40 years. You will correspond with them; you will be dependent on them for your reputation; and if you are ever honored, in the fullness of time, it will be they who proffer the honor.

It is possible to attend too many meetings, and this can take your scanty free time for a year. For each meeting attended, count a week or 10 days; for each at which you give a report, you must count much more. You can easily find yourself preparing papers, talks and reports for organizations to the extent that all your free time for new work is lost.

Once at the meetings, meet the men and listen to the papers. The latter can be hard work, but it is crucial, since a year can elapse before a paper is published, and you can't afford to be a year behind.

What is good enough for a report is adequate for a publication, so write the thing up while it is still fresh, and send it to the appropriate journal. I think it is well to select just the right journal and to send most of your original work to it. However, some believe in diversifying their media, and this may be a good idea. Ordinarily, one reports on each new work only at one society and publishes the findings only once. Some of our colleagues have developed the art of forcing each new fact to serve for many by publishing disguised rewrites, but they soon earn a reputation for this. In fact, there are many devices which our more "pushy" confreres use to further their notoriety; however, in the end, I think it would be better if your name at the head of a paper became, in your group, the hallmark of a new and original piece of work.

With that parting thought, I shall say,

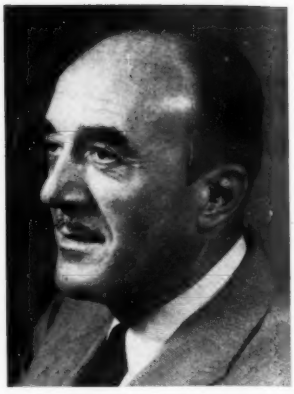
Good night,
Father

Special Issue
NOVEMBER 1959

New York University-Bellevue Medical Center

Postgraduate Medicine

Introduction



GEORGE E. ARMSTRONG

WE at the New York University-Bellevue Medical Center felt deeply honored when the Editors of POSTGRADUATE MEDICINE asked us to sponsor one of its issues. This sponsorship having been mutually agreed on, I should like to take this opportunity to give a brief history of the Medical Center, one of the newer centers in this country.

One question which I encounter frequently and which, therefore, I should like to explain initially concerns the apparent anomaly found in the Center's official designation, which couples the medical element of a large private university with one of the oldest and better-known municipal hospitals. The answers in brief are: The New York University College of Medicine has utilized Bellevue Hospital as a source of clinical teaching and research for more than a century. At one time Bellevue Hospital had its own medical school, which merged with the New York University College of Medicine shortly before the turn of the century. The Bellevue Schools of Nursing also operate under the aegis of our College of Medicine. In addition, geographic contiguity has facilitated this association.

When the Medical Center came into being, following the merger with New York University Post-Graduate Medical School and Hospital late in 1948, the University and New York City collaborated in many of the physical details of the new Center campus, such as contiguous streets and parking plans, and the erecting by the City of New York of a new building for Forensic Medicine now under construction on ground deeded to the City by the University.

The Center itself includes the College of Medicine, the Post-Graduate Medical School, the University Hospital and its Institute of Physical Medicine and Rehabilitation, Alumni Hall (with an auditorium which accommodates 500 persons and with classrooms for 350 students), a hall of residence housing 400, and the Henry W. and Albert A. Berg Institute for Experimental Physiology, Surgery and Pathology.

Now in its twelfth year, all of the Medical Center buildings have been completed with the exception of the new University Hospital, now under construction. The buildings, representing a capital investment of about $50 million, represent the most modern facilities for medical education at all levels as well as all types of medical research and patient care.

Located as our Medical Center is on the eastern side of mid-Manhattan, it is easily reached by visitors to New York City, and a warm invitation is extended to the readers of POSTGRADUATE MEDICINE to visit us whenever the opportunity arises.

GEORGE E. ARMSTRONG, M.D.
Director, New York University-Bellevue Medical Center, and Vice President for Medical Affairs, New York University

The Dean's Message

DONAL SHEEHAN

We are pleased to join the ranks of the distinguished institutions which have had special issues of Postgraduate Medicine devoted solely to the work of their medical staffs and faculty members. It is our hope that the subject matter covered herein will convey to the readers at least a portion of the activities of the faculty of New York University-Bellevue Medical Center, and that it will also prove helpful to those who are concerned primarily with the general practice of medicine.

As our Director, Dr. Armstrong, has pointed out, our Medical Center (as presently organized) is young in years, but it is comprised of institutions rich in experience and tradition. Our aim is to keep the best of the past and to strive ceaselessly to better today's best. The key to accomplishing this goal lies in the hands of our faculty members, who have more than demonstrated their willingness to accept this challenge.

I should like to express my appreciation to our guest editor, Dr. Steele, for compiling this issue and to the representatives of our faculty who have contributed to its pages. Our special thanks go to the Editors of Postgraduate Medicine for giving us this welcome opportunity to present these contributions to the many physicians who constitute the readership of their splendid publication.

Donal Sheehan, M.D., *Dean,*
New York University College of Medicine and
New York University Post-Graduate Medical School

Foreword

J. MURRAY STEELE

To write a word or two as a foreword to this issue is a privilege that, at the same time, presents certain difficulties because of the variety of the material to be presented. The volume as a whole is perhaps best considered as illustrating some of the fields of interest of the faculties of the New York University College of Medicine and of the New York University Post-Graduate Medical School. The range is wide, and it extends from dermatology through various phases of heart disease and electrolyte disturbances to orthopedic surgery, anesthesia, psychiatry and forensic medicine. We hope that the variety of subjects taken up will make this special issue as interesting to readers as have been earlier special issues from other institutions. An effort of this nature may characterize to a certain extent the institution concerned in a way that annual brochures or catalogues are not apt to do. We hope that the material will be found useful as well as informative of the program at New York University-Bellevue Medical Center.

We should like to add that the task of collecting and editing these articles was made much lighter by our Office of Development and Public Relations, which acted as the clearinghouse for the collection of these manuscripts and assured their delivery in time for the issue to go to press.

J. MURRAY STEELE, M.D.
Professor of Medicine, New York University College of Medicine
GUEST EDITOR

Managing Unmanageable Edema

EUGENE Y. BERGER*

New York University College of Medicine, New York

Edematous patients, irrespective of the concurrent disease, either maintain their weight from day to day and excrete sodium in the urine or gain weight and do not excrete sodium. Two simple tests to identify the patient with edema refractory to conventional therapy are to determine the rate of daily weight gain referable to intake of salt and to analyze the urinary sodium. Procedures advocated to overcome refractoriness to mercurial diuresis are designed to increase the sodium delivered to the distal portion of the nephron or to create a proper electrolytic milieu for mercurial action. Use of steroids appears empirical.

EUGENE Y. BERGER

THIS discussion concerns dropsy and how it can be treated, sometimes with success. "The term dropsy may be used to denote either an increased amount of fluid in the connective tissue spaces, especially of the skin, when it is sometimes designated as anasarca or oedema, or an accumulation of fluid in the serous spaces of the body, as in the conditions of hydrothorax and ascites." So wrote Starling[1] in 1909. On the semicentennial of this writing, the term dropsy has fallen into relative disuse. In 1959, "edematous patient" has taken on a connotation which includes hydrothorax and ascites.

The discussion to follow applies, except as noted, to the treatment of edema without respect to the associated disease (usually congestive heart-failure or cirrhosis of the liver). Our present concern is the edematous patient who fails to respond to conventional methods of therapy and who is considered to have refractory edema. "Refractory" is used in the sense of resisting ordinary treatment. A patient who can be managed with a mercurial diuretic once or twice a week is not the one who is under discussion.

Starling defined the forces which determine the two-way flow of fluid across the capillary wall, from the circulating plasma to the interstitial space at the arterial end of the capillary and from the interstitial space to the circulating plasma at the venous end of the capillary. One force is the difference in hydrostatic pressure across the capillary wall, with the pres-

*Assistant Professor of Medicine, New York University College of Medicine; The New York University Research Service; Goldwater Memorial Hospital, Welfare Island, New York, New York.

sure inside the capillary acting on one side and the tissue turgor on the other. The second force is the osmotic pressure. The interstitial fluid contains little protein compared with the plasma and hence has a lower osmotic pressure. The normal capillary wall is relatively impermeable to protein, and the difference in protein concentration across the capillary wall creates an osmotic pressure gradient which is a force against the transudation of fluid but favors the entry of fluid into the vascular compartment. Starling pointed out that the interstitial fluid may also return to the circulation by way of the lymphatics. The osmotic and hydrostatic pressures, the integrity of the capillary wall, and the lymphatic system are all factors which determine the transfer of fluid into or out of the interstitial space. A disturbance of any one of these usually leads to edema, and in any given patient with edema more than one factor usually is involved.

Two examples will serve to illustrate Starling's hypothesis. A patient who is awakened at night with paroxysmal nocturnal dyspnea has transudation of fluid into the alveoli because of the increased hydrostatic pressure in the pulmonary capillaries, and the rate of transudation of fluid from the capillary exceeds its return to the vascular compartment. There is a redistribution of body fluid, and only a small amount of fluid (500 ml.) may be involved in this transfer, but there is no net gain in weight from the time the patient went to bed. A patient with thrombophlebitis and swelling of a limb has transudation of fluid into the interstitial spaces because of increased capillary hydrostatic pressure caused by the obstruction in the vein. In addition, the altered integrity of the capillary wall and the impeded return flow of fluid through the inflamed lymphatics favor the formation of edema. Transudation of fluid into the interstitial spaces will occur, and edema will increase in thrombophlebitis until the aforementioned forces come into equilibrium.

There are clinical conditions, nonetheless, in which edema fluid continues to accumulate far beyond the point of equilibrium of pressures across the capillary wall. These clinical states arise when the kidney fails to excrete salt in amounts equal to the dietary intake. With the retention of salt, the body fluids do not turn to brine and the patient does not become pickled; rather, there is an equivalent retention of water diluting the retained sodium and thus maintaining the existing sodium concentrations. The patient may consume potassium, ammonium or calcium chloride with impunity, and sometimes even benefit, but the intake of sodium chloride or sodium bicarbonate—or, for that matter, almost any salt containing sodium—will immediately lead to further edema. Although the edematous patient may excrete water more slowly than normal,[2-5] the fact is that he eventually does excrete it. Indeed, a large intake of water has been advocated for the treatment of edema.[6,7] The practice of limiting the intake of fluid in congestive heart-failure began to fall into disuse in this country in the early 1940s with the publication of Schroeder's work. He demonstrated that a sodium intake permitted unrestricted fluid intake without a *pari passu* rise in edema formation.[8,9] Sodium is now accepted as the culprit, and most observers agree that the retention of water is a secondary phenomenon. However, why the kidney fails to excrete dietary sodium in expected amounts is by no means agreed upon.

Many factors are known to affect the renal excretion of sodium. A wealth of publications exist, particularly in regard to congestive heart-failure, explaining why the kidney retains sodium, and theories, backward and forward, have been propounded.[10-20] The disordered Starling equilibrium, itself, is thought to be a step in inducing sodium retention by the kidney.[21,22] Alterations in glomerular filtration rate,[23] renal arterial and venous pressure,[24-26] oxygen tension in blood,[27] plasma volume,[28] and the mineralocorticoid activity[29-33] all have been demonstrated to alter the renal excretion of sodium in normal subjects and laboratory animals, and comparable abnormalities have been shown to exist in edematous states. The controversy, then, is a very human one, and lies specifically in one of two areas: (1) separating the important from the unimportant, or (2) deciding which one of the many factors came first—the chicken or

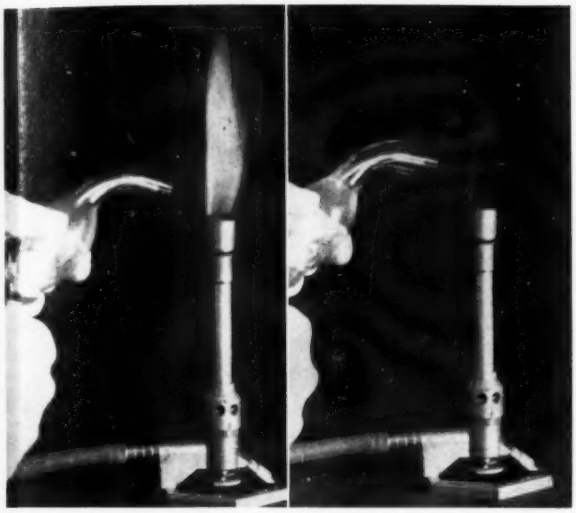


FIGURE 1. A few drops of urine have been placed in a DeVilbiss No. 40 nebulizer and sprayed into the blue flame of a Bunsen burner. On the left, the urine of a patient with cirrhosis of the liver and mild edema causes the flame to flash bright yellow; the urine contained 30 mEq. of sodium per liter by analysis. For comparison, on the right, the urine of a patient with cirrhosis, ascites and massive edema barely changes the color of the flame; the urine contained 1 mEq. of sodium per liter.

This simple procedure may be made semiquantitative by matching colors with a set of standards of known concentrations of sodium. If a Bunsen burner is not at hand, one may use the blue flame from a self-contained propane or butane torch (a small one may be obtained at a hardware store), from a cigarette lighter filled with alcohol (the Zippo lighter works quite well), or from the kitchen gas burner.

the egg. Although I favor the importance of the hormonal disturbance,[30,34] I will not concern myself with the reasons why. Faced with the fact that the kidney retains salt abnormally, the question is what can be done.

The Patient With Refractory Edema

To identify the patient with refractory edema, there are two simple tests: (1) the rate of daily weight gain referable to the salt intake, and (2) an analysis of urinary sodium.

A patient gaining a pound or two per day in weight gains 500 to 1000 ml. of extracellular fluid containing 65 to 130 mEq. of sodium (these patients usually are hyponatremic). This represents an intake of roughly 4 to 8 gm. of sodium chloride over and above the excretion (0.9 per cent saline contains 9 gm. of sodium chloride per liter equivalent to 155 mEq.). The patient, of course, may deny eating this much salt, but there is no other way progressively to put on a pound or two per day in weight, except by dilution of body fluids, which cannot continue for very long.

The second test of refractory edema is the concentration of urinary sodium. If it is 25 or 50 mEq. per liter, and the patient is excreting a liter of urine per day, he is not refractory to therapy. He can generally be kept edema-free by (1) limiting sodium intake, (2) if in congestive heart-failure, insuring adequate digitalization, and (3) diuretic therapy, such as organic mercurials, chlorothiazide, and so on, to which these patients usually are responsive. If the edema fails to subside in the patient who is excreting sodium, the stumbling block lies in the mechanics of administering conventional therapy. For example, a patient who is cautioned about eating food with high salt content is discovered to be taking sodium bicarbonate for stomach distress. The patient who remains seated in a wheel chair, failing to move the lower extremities because of malum coxae senilis or an ischemic ulcer of the heel, may develop extensive edema of the lower extremities, unmoved by diuretics or elevation of the extremities in the chair. This patient, if put to bed and the foot of the bed frame elevated to an angle of 20 or 30 degrees, may very likely have a massive diuresis. It is the patient with a urinary sodium concentration of less than 1 or 2 mEq. per liter who presents the problem of refractory edema.

It is, of course, ideal to have laboratory facilities to determine urinary sodium concentrations, and many laboratories have flame photometers for doing so. However, a simple quantitative test for sodium is sufficient to identify the patient who is excreting less than 1 mEq. per day. Everyone has had the experience of spilling salt in a blue gas flame and seeing the flame turn yellow. The more

salt added, the deeper is the yellow color. The flame photometer is a device which regulates the delivery of properly diluted solutions of sodium salt into the flame and measures the depth of color with a photoelectric cell.

In the absence of a flame photometer the eye may serve as the photoelectric cell, and a hand nebulizer (DeVilbiss No. 40) has the correct rate of delivery so that dilution of urine is unnecessary. When a specimen of undiluted urine is sprayed from the nebulizer into a blue flame, the flame will flash bright yellow if the sodium concentration is more than 25 mEq. per liter. There will be some yellow color with concentrations of 5 to 10 mEq. per liter, and the flame will barely change if the sodium concentration is less than 1 mEq. per liter (figure 1).* Knowledge of the urinary concentration of sodium on a day when the patient has not received a diuretic agent alerts the clinician to the degree of refractoriness of the patient's edema.

Diuretic Therapy

The treatment of the patient with intractable edema identified by either of the two tests already described is not a cheerful prospect. The ascitic fluid, pleural fluid, or edema fluid in the lower extremities can be removed temporarily by paracentesis, thoracentesis or the use of Southey's tubes, only to reaccumulate. Limitation of dietary sodium will certainly retard the rate of accumulation, and if the patient can be induced to limit his intake to rice and fruit juice he may maintain his *status quo*.[35] The problem, however, is to induce the kidney to excrete the retained excess sodium. In these patients organic mercurials usually fail to produce a satisfactory response.

The many procedures that have been advocated to turn a mercurial-refractory kidney into a responsive one may be classified into three general categories: (1) those aimed at increasing the amount of sodium delivered to the distal portion of the nephron, (2) those designed to create a setting of electrolytes where mercurial diuretics work best, and (3) those employing steroids, which, for the present, appear empirical.

Increasing the sodium load to the kidney tubule—The amount of sodium delivered to the distal tubule may be increased by elevation of the filtration rate. Weston[36] has advocated the use of intravenous aminophylline (0.48 to 0.72 gm.) at the height of the mercurial stimulation (one to two hours after the mercurial injection). This procedure has been recommended for the patient with congestive heart-failure, in which the glomerular filtration rate is decreased. But for the patient with decompensated cirrhosis of the liver, in which the filtration rate usually is normal or elevated,[37] aminophylline probably is of little use.

Bernstein and associates[38] delivered increased amounts of sodium to the distal nephron in six patients by intravenous administration of 25 per cent mannitol (up to 2000 ml. over four to eight hours) and combined intravenous mercaptomerin (THIOMERIN®) with the osmotic diuretic. Four patients had satisfactory diuresis. One with nephrotic edema lost 8½ lb. and had no ill effects; two with congestive heart-failure lost 8½ and 9½ lb., respectively, but pulmonary edema developed; the fourth patient, with cirrhosis of the liver, lost 11½ lb., and "central nervous system symptoms of hepatic insufficiency" developed.

Creating the proper milieu in the kidney—If hypochloremia develops during the use of mercurial diuretics, the patient usually is unresponsive to further use of mercury.[39] Ammonium chloride will replace the lost chloride. The ammonium is metabolized to urea by the liver, and the excess chloride can be excreted by the kidney with sodium, potassium and, as time goes by, ammonium which the kidney supplies from amino acids. If ammonium chloride is used to potentiate mercurial diuresis, uninterrupted therapy is preferred. Interrupted therapy may also be used. It does not seem to matter whether ammonium chloride is administered for a few days before or after the mercurial, so long as the hypochloremia is corrected. Enteric-coated tablets are frequently useless, but uncoated tablets or an elixir of ammonium chloride may be effective in turning

*A kit containing nebulizer, self-contained burner, and a set of standards is available from Metro Industries, 11-38 Thirty-first Avenue, Long Island City 6, New York. Catalogue No. ME 3400.

a mercurial-refractory patient into a responsive one. It is surprising how often the uncoated tablet or the elixir may be used without gastrointestinal disturbances.

Acetazolamide (DIAMOX®) creates hyperchloremia, not by replacement of chloride but by causing an initial loss of bicarbonate which is not replaced as long as acetazolamide is continued.[40] When acetazolamide (750 mg. daily) is administered with ammonium chloride (8 to 10 gm. daily), the hypochloremic effect of each drug is summated, and, reportedly, a larger diuresis will ensue after administration of a mercurial than when either one is used by itself.[41]

The use of cation exchange resin in the ammonium or hydrogen cycle may also correct hypochloremia, not by adding chloride, as with ammonium chloride, or by depleting bicarbonate, as with acetazolamide. The resin, by depleting the patient of sodium and potassium, will create a relative excess of chloride. Quite often, cation exchange resin will potentiate a mercurial diuretic to a greater degree than will ammonium chloride (table 1). Mudge and Hardin[42] demonstrated that feeding sodium bicarbonate to dogs gives rise to alkalosis, and mercurial resistance develops. When the same degree of alkalosis is induced by potassium-deficient diets the dogs will respond to meralluride (MERCUHYDRIN®) with normal or increased diuresis. Mudge and Hardin pointed out that a low potassium diet will lead to hypokalemic alkalosis but the alkalosis is confined to the extracellular fluid, whereas the intracellular fluid is acidotic. The edematous patient receiving cation exchange resin in the ammonium or hydrogen cycle not only develops extracellular hyperchloremia and acidosis but also is potassium-deficient;[43] both factors potentiate the action of mercury.

The use of cation exchange resins to potentiate mercurial diuretics has been quite satisfactory in our experience, but it is by no means a panacea for intractable edema. The attitudes of both the patient and the physician are involved; the patient must be sick enough to "take anything" and the physician enthusiastic enough to convince him to do so. The acidosis is without clinical effects. The depletion of potassium leading to plasma potassium levels below 3 mEq. per liter occurs without clinical symptoms in the patient with cirrhosis of the liver (in the case represented in table 1, for weeks), but signs of digitalis toxicity may develop in the patient with congestive heart-failure receiving digitalis. In the patient with cirrhosis of the liver, hepatic coma is a danger with ammonium carboxylic resins,[44,45] but prior to the publication of this information in 1952, patient M. H. (table 1) received ammonium chloride or ammonium resin from May 1949 to May 1950 without a single episode of coma. A history of coma would be a contraindication to the use of ammonium exchange resins.

The refractory patient with edema and congestive heart-failure or cirrhosis of the liver is commonly hyponatremic. The term hyponatremia itself contributes to the confusion about the syndrome of hyponatremia. This syndrome should more properly be called hydremia, for the disturbance is one of water and the antidiuretic hormone rather than one of sodium. The intake and excretion of water largely determine the concentration of sodium in extracellular fluid, whereas the intake and excretion of salt largely determine the total amount of extracellular fluid.[46] Correction of the hydremia by no means insures a satisfactory diuresis after mercurials. Our experience with infusing hypertonic saline or salt by mouth has been, with a few exceptions, uniformly bad. These patients seem to have their osmometers set at a given low level of sodium. If salt is administered and water withheld, serum sodium rises, but more often sooner than later the patient manages to get his glass of water, serum sodium returns to where it was to begin with, and the patient is so much heavier. More distressing is the fact that administration of hypertonic salt solution not infrequently is followed by the death of this admittedly sick patient. After the infusion of hypertonic saline, seven of seven patients with congestive heart-failure reported by Uricchio and Calenda[47] died, and three of three patients reported by Griffith and Magidson.[48]

Determination of the concentration of sodium in the plasma in the edematous patient is

TABLE 1

COMPARISON OF THE EFFECT OF AMMONIUM CHLORIDE AND CARBOXYLIC RESIN IN THE AMMONIUM CYCLE ON MERALLURIDE (MERCUHYDRIN) DIURESIS*

DATE	AMMONIUM CHLORIDE *(Grams per 24 hours)*	CARBOXYLIC RESIN *(Grams per 24 hours)*	MERALLURIDE *(Milliliters)*	WEIGHT CHANGE *(Pounds per 24 hours)*	URINE VOLUME *(Milliliters per 24 hours)*	URINARY SODIUM *(Milliequivalents per 24 hours)*
May 11, 1949	0	0	2	+2¼	1,280	14
August 7, 1949	5.8	0	3	−2½	3,230	173
August 18, 1949	0	45	3	−7	6,310	476

*M. H., a 46 year old man with decompensated cirrhosis of the liver and abdominal ascites. Ammonium chloride (uncoated 5 gr. tablets) was started June 5, 1949, and discontinued August 12, 1949, when carboxylic resin in the ammonium cycle was substituted. Resin dosage was adjusted so that the amount of ammonium administered was equivalent to that administered with ammonium chloride (109 mEq.).

of limited value compared with knowledge of the urinary excretion of sodium. More information about the clinical status of the patient can be obtained from the urinary sodium concentration than from the plasma sodium concentration, for example, whether the edema is of the refractory variety, whether a diuretic agent is causing a natruresis, and so on. A laboratory report of a low plasma sodium in an edematous patient means the hand of the house officer armed with this information must be stayed lest he administer hypertonic saline with a deleterious effect on the patient.

Steroids—While there is some rationale for the use of aminophylline, ammonium chloride or cation exchange resin to potentiate the action of mercurials, for the present there is no good reason to give corticotropin (ACTH) or steroids, except for the fact that they may work. Patients resistant to mercurial diuretics have been made responsive by the prior administration of ACTH,[49, 50] prednisone,[51, 52] steroidal lactones,[52] and 6-methylprednisolone (with chlorothiazide instead of mercury).[53]

TABLE 2

EFFECT OF ORAL ADMINISTRATION OF 9-ALPHA-FLUOROHYDROCORTISONE ACETATE ON MERCURIAL DIURESIS*

DATE	9-α-FLUOROHYDROCORTISONE *(Milligrams)*	MERCURIAL DIURETIC *(Milliliters)*	URINE VOLUME *(Milliliters per 24 hours)*	URINARY SODIUM *(Milliequivalents per 24 hours)*
March 10 (1955)	0	0	580	1.1
March 11	0	2	780	20.0
March 12	0	0	390	0.6
March 13	0	2	1,010	44.8
March 14	1	0	405	0.8
March 15	3	0	390	0.6
March 16	3	0	320	1.1
March 17	3	0	400	0.6
March 18	3	0	440	0.6
March 19	0	0	460	0.6
March 20	3	0	460	0.6
March 21	3	0	500	0.6
March 22	3	0	440	0.6
March 23	3	0	340	0.5
March 24	3	0	400	0.7
March 25	1	0	310	0.7
March 26	0	2	4,420	410.0

*E. M., a 25 year old woman with rheumatic heart disease, cardiomegaly, mitral stenosis and insufficiency, atrial fibrillation, pulmonary edema, hepatomegaly, ascites, sacral edema, and edema of both lower extremities.

The dosage schedule is somewhat arbitrary. Camara and Schemm[49] used 10 to 25 mg. of ACTH intramuscularly every six hours for 10 to 12 days in congestive heart-failure. Riemer[51] used 2.5 mg. prednisone by mouth three times a day for more than 250 days in one case of congestive heart-failure. Morrison and Chalmers[52] used 10 mg. of prednisone by mouth every eight hours or 100 mg. of spirolactone by mouth or intramuscularly every eight hours in patients with cirrhosis of the liver and ascites whose base-line sodium excretions were less than 1 mEq. per day. Redeker and associates[53] used 6-methylprednisolone in a dosage of 12 mg. a day with 2 gm. of chlorothiazide a day in patients with cirrhosis of the liver.

The most potent salt-retaining steroid known, 9-alpha-fluorohydrocortisone, also potentiates a mercurial diuresis in an otherwise refractory patient (table 2). The patient represented in the table was excreting negligible amounts of sodium in the urine, so that the sodium-retaining effects of the drug could not harm her clinical course. In patients who excrete more than a few milliequivalents per 24 hours, 9-alpha-fluorohydrocortisone is most certainly contraindicated. Prednisone has minimal salt-retaining qualities compared with 9-alpha-fluorohydrocortisone, yet both steroids potentiate mercurial diuresis in those patients who are otherwise refractory.

In regard to the mode of action, my favorite notion, if incorrect, is that during the period steroids were administered the patient did not have to ingest 18 uncoated 5 gr. tablets of ammonium chloride or 45 gm. of carboxylic resin each day but instead could have three meals a day, and the patient rather than the physician adjusted the electrolyte milieu in the kidney. When a mercurial diuretic was administered, the correct intracellular pH existed in the nephron for the cellular dithiols to unite with the organomercurial and happily a diuresis ensued.[42]

Electrolyte losses during mercurial diuresis—A few remarks should be made at this point as to the nature of the electrolyte losses if the refractory patient does have a satisfactory diuresis after mercury. Lesser and co-workers[54] estimated the electrolyte losses following the administration of a mercurial diuretic in edematous patients who without a diuretic excreted less than 1 mEq. of sodium per day. The concentrations of chloride, sodium and potassium in the diuretic urine were, respectively, 151, 97 and 35 mEq. per liter (means of 75 diureses with an increase of at least 1000 cc. over the previous day's output). The significance of the urinary losses of these ions can be interpreted in terms of the clinical picture which follows mercurial diuresis in edematous patients. The urine lost is isotonic with edema fluid, as evidenced by the chloride concentration, but the composition of this diuretic urine is quite different from that of the edema fluid. Chloride is lost in concentration of 151 mEq. per liter from edema fluid containing 100 to 110 mEq. per liter. Relatively more chloride is lost than water, with a resultant fall in plasma chloride and production of a metabolic alkalosis. The sodium concentration in the diuretic water is 97 mEq. per liter, lost from edema fluid at 130 mEq. per liter. In this instance more water is lost than sodium, and theoretically sodium concentration should rise. It does rise if water intake is limited, and this is the basis for the correction of hyponatremia by controlled use of mercurials.[55] Potassium concentration is considerably higher in diuretic urine than in edema fluid, and potassium losses are so great that the potassium, of necessity, must come from intracellular sources. (In all probability the intracellular potassium is replaced by sodium which did not appear as a rise in extracellular sodium concentration.) Normal persons do not lose potassium after a mercurial diuretic,[56] but the potassium losses in the edematous patient may reach 200 mEq. in 24 hours.[54] The weakness and nausea following a large diuresis, usually attributed to sodium depletion,[57,58] are more likely caused by potassium loss.[54] Likewise the arrhythmias occurring in digitalized patients after a mercurial diuresis, usually attributed to mobilization of digitalis from edema fluid,[59-61] may be explained by potassium loss.[54]

To summarize the electrolyte losses during mercurial diuresis, the sodium losses in edematous patients who otherwise excrete less than

1 mEq. of sodium per day tend to produce hypernatremia; the chloride and potassium losses produce metabolic alkalosis and potassium deficiency. (For further details and variants of the electrolyte losses after mercurial diuresis, the reader is referred to a most comprehensive study by Schwartz and Wallace.[39])

Other diuretics—Acidifying salts (ammonium chloride and calcium chloride), xanthines (caffeine, theobromine, theophylline), osmotic diuretics (urea and dextrose[62]), aminouracils (MICTINE®), and carbonic anhydrase inhibitors (acetazolamide [Diamox][63, 64]) are of little practical value in refractory edema by themselves except possibly to set the stage for mercury.

One of the more recently introduced carbonic anhydrase inhibitors, chlorothiazide (DIURIL®), merits more detailed discussion. Like other carbonic anhydrase inhibitors it causes an increase in bicarbonate excretion, but in addition it causes a chloruresis. Its clinical effect is that of chloride loss rather than bicarbonate loss. Although both mercurials and chlorothiazide cause a chloruresis, the sites of action are different. When chlorothiazide and the mercurial chlormerodrin (NEOHYDRIN®) are administered together intravenously to the dog in doses which individually produce maximal effects, the combination produces a response greater than the maximum obtainable from either alone.[65] Dimercaprol (2,3-dimercaptopropanol, British anti-lewisite, BAL) does not block the action of chlorothiazide, but the same dose will reverse the diuretic effect of meralluride (Mercuhydrin).[66] Despite these differences in the site of action, chlorothiazide and mercurials have similar effects clinically. Chlorothiazide has the advantage of prompt and complete absorption from the intestine, and the time of onset of the diuresis after oral administration of chlorothiazide is close to that of intravenous mercurial diuretics.[67] Schreiner and Bloomer[68] pointed out that chlorothiazide may be less toxic than mercurial diuretics in active renal disease. Chlorothiazide has been reported to be effective in edema of heart-failure, nephrosis and cirrhosis, where the same patient was refractory to mercurials.[69-71] When a mercurial diuretic and chlorothiazide are administered together, an increased response to the mercurial diuretic (or chlorothiazide) may occur.[70, 71] With these advantages, the oral administration of 1 gm. of chlorothiazide may eventually supplant the 2 cc. of a parenteral mercurial diuretic for the therapy of "run-of-the-mill" edema. However, in regard to the patient with refractory edema, Kennedy[72] presented observations on five patients with congestive heart-failure who were excreting less than 1 mEq. of sodium per 24 hours in whom chlorothiazide was almost totally ineffective, while mercaptomerin (Thiomerin) produced a natruresis. Sherlock and co-workers[73] made a similar observation in two of five patients with ascites due to cirrhosis.

Summary

The therapy of refractory edema, by definition, is not commonly successful. In the following summary of diagnosis and therapy the reader is asked to bear with oversimplifications and dogmatism, two invaluable aids in complicated, uncertain circumstances.

The edematous patient, irrespective of the concurrent disease, can be categorized into one of two groups: (1) those who maintain their weight from day to day and excrete sodium in the urine, and (2) those who gain weight from day to day and do not excrete sodium in the urine.

If the edematous patient excretes sodium in the urine he can be managed by conventional therapy.

If the edematous patient has negligible amounts of sodium in the urine, one of the following forms of treatment may be tried to set the stage for a mercurial diuresis: (1) use of aminophylline intravenously one or two hours after the administration of a mercurial diuretic (in congestive heart-failure); (2) administration of uncoated tablets of ammonium chloride or a daily dosage of 6 gm. of an elixir of ammonium chloride; (3) administration of absorbable ammonium chloride and 750 mg. of acetazolamide; (4) administration of 30 to 45 gm. of carboxylic resin in the hydrogen cycle, or (5) administration of prednisone in a dosage up to 30 mg. daily.

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Nerve Blocking

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The use of nerve blocking to diagnose or treat pain has not received a fraction of the interest shown in regional anesthesia in surgical practice. In view of the optimistic results of therapeutic nerve blocking not only to relieve pain but also to arrest physiologic disturbances, a plea is made for greater appreciation of its advantages, more energetic exploration of its possibilities. Certainly in intractable pain if some type of physiologic nerve section is possible it should have precedence over addicting drugs or radical and often mutilating surgical procedures.

E. A. ROVENSTINE

NERVE blocking, a contribution of medical science toward the control of pain, has, in a comparatively short time, outgrown its original function. Proposed and developed largely as an aid for surgical anesthesia, nerve blocking has grown to become a new compartment of knowledge. Every branch of medicine has been affected by the growth of this technic. Designed primarily as an aid in or substitute for inhalation narcosis during surgical procedures, it is now being used with increased frequency to eliminate the need for surgery.

With the extension of these practices, the single designation and the terms to describe certain phases, such as local, conduction and spinal anesthesia, were inadequate. "Nerve blocking" became more popular. "Diagnostic nerve block" was introduced to designate an anesthetic procedure which would temporarily control nerve impulses to permit a differentiation of one condition or complaint from another. "Prognostic nerve block" designated use of temporary regional anesthesia to foretell what might be expected from permanent destruction of the pathways involved. "Therapeutic nerve block" was the term given to procedures which cured a disease or relieved symptoms.

Nerve blocking has invaded more than the practice of diagnosis, prognosis and therapy. It has come to play a significant role in preclinical fields. Its technics have made possible experimental studies, new concepts, and far-reaching discoveries in physiology, pharmacology and anatomy.

History

The remarkable growth and development of regional anesthesia as a new field of knowledge, or an extension of the already existing practice of surgical anesthesia, have come about

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within a relatively short time. A history of the subject can be compiled by living pioneers who have seen it evolve and unfold during their practice of medicine. This fact is significant evidence of the rapid progress of modern scientific achievements and the speed of present-day advances in medical practice.

Nerve blocking, like all things new in medicine, was no spontaneous innovation created suddenly by genius or accident. It was born of knowledge accumulated during many years, the experiences of searching investigators, and the ingenuity of human invention.

A most important tool of science, the syringe, was proposed to fill a need for an instrument that would permit the introduction of a clotting solution into an aneurysm. Dr. Charles Gabriel Pravaz of France invented the hypodermic syringe in 1851 to be used for that purpose. The following year his improved hypodermic syringe made from silver became popular for hypodermic medication. Before Pravaz (as early as 1826), Lembert, also of France, had suggested that medicaments should be introduced under the skin, and two years later his countryman LaFarque began making punctures over painful areas and plugging them with pellets of morphine. In 1845 Francis Ryan of Dublin invented a trocar with a removable cannula and a gravity flow device to introduce sedative drugs into the subcutaneous tissues.

In 1855, four years after the Pravaz instrument was designed, Alexander Wood independently introduced the hypodermic syringe and needle for the relief of pain with opium and morphine. He injected the drugs into tissue so that they would come into intimate contact with nerves in the painful area. Following Wood's experiments and experiences the local injection of solutions was practiced with decreasing enthusiasm for several years. Attempts to obtain local anesthesia during minor operations were only partially successful, but the syringe was popular for introducing drugs quickly and directly into the circulation. Charles Hunter (1861), who gave the name hypodermic to the subcutaneous method, did much to popularize the procedure in England and reported on the use of chloroform injections for local anesthesia. Fordyce Barker (1856) was among the first to use the hypodermic syringe in America. In 1864 Albert Eulenburg of Germany excised a papilloma of the vocal cord without pain or spasm of the glottis after injecting the superior laryngeal nerve with a solution of morphine.

The second discovery to set the stage for the rapid development of regional anesthesia came in 1884. In September of that year, Karl Koller reported to the German ophthalmologic society of Heidelberg on the use of cocaine as an anesthetic in surgery of the eye. This momentous discovery of a new use for cocaine spread rapidly. C. Stedman Bull was first to use it in America, and before the end of the year many reports of topical-application anesthesia were in print. The first premeditated use of the anesthetic (1884) for regional anesthesia must be credited to W. S. Halsted, who, working at Bellevue Hospital in New York with R. J. Hall, originated the principles of nerve blocking and performed amputations after brachial plexus block, extractions after infra-orbital block, and more than a thousand similar regional anesthetic procedures within a year after Koller's report.

In 1885, J. Leonard Corning of New York announced the important fact that cocaine's action could be greatly prolonged by reducing the circulation in the anesthetized area. This contribution had wide significance after Braun of Germany introduced the use of epinephrine in 1901. Corning has priority in epidural and subarachnoid injections of cocaine, although the latter procedure was rediscovered and popularized by Bier 14 years later (1899).

Further advances in nerve blocking came about with new and refined technics and more liberal application to an increasing number of regions of the body. Substitution of the less toxic, synthetic eucaine (1898) and later procaine (Einhorn, 1905) for the alkaloid cocaine added to the safety of nerve blocking. Since 1910 the significant discoveries and improvements in the field of regional anesthesia have followed one another so rapidly from experimental laboratories of the preclinical sciences, from the laboratories, wards and operating rooms of the clinical sciences, and

from the great laboratories of commerce that a recital of their contributors and the nature of their importance would supply material for a lengthy monograph.

Nerve Blocking

Nerve blocking to provide surgical anesthesia has eclipsed by far similar procedures employed to cure or alleviate pain or symptoms resulting from disease or injury. Nerve blocking, when it came into being, found a large number of enthusiastic surgeons to explore its possibilities, exploit its application, and evaluate it in surgical practice. Its use for other than surgical anesthesia had no such generous reception. It has not received even a small fraction of the experimental or clinical investigation accorded the application of physiologic nerve section for surgical procedures. Only in recent years has real enthusiasm been shown for blocking peripheral nervous pathways to diagnose or treat pain. Even now the development and inevitable improvements of this practice suffer from lack of interest, and its evaluation still awaits the final test of liberal clinical application.

It is likely that inhalation anesthesia, developed during the latter part of the nineteenth century and still in a stage of uncertainty in 1885, did not really retard the experimental and clinical efforts to use hypodermic injections for surgical anesthesia. It is evident, however, that surgery was not ready to give an all-out effort to any anesthetic method until near the end of the nineteenth century when the antagonism to Lister's antisepsis was overcome and the fear of infections banished. Halsted related in an interesting fashion his experiments in 1884 and 1885 with injecting the trunks of nerves supplying affected parts to permit surgery. Much of this work was done in a large tent erected near Bellevue Hospital in New York, since it was "impossible to carry out antiseptic precautions in the general amphitheatre at Bellevue where numerous anti-Lister surgeons dominated and predominated." Opposition to antisepsis was definitely overcome before the turn of the century. In practically all surgical centers, dry heat and steam sterilization had replaced chemical antiseptics, and the stage was thereby prepared for the use of the hypodermic syringe to bring a solution of cocaine as an anesthetic agent into contact with unexposed nervous tissues.

Therapeutic Nerve Blocking

Although therapeutic nerve blocking is an outgrowth of regional analgesia utilizing the same anatomic and physiologic principles and has therefore an identical historical development, it can be said to have come into actual existence and to have gained recognition as a therapeutic measure during the last three score years. This belated arrival of a procedure with so much promise is not readily understandable. Its use in the important conquest of pain is entirely logical since its primary role, the control of pain from chronically diseased and injured tissues, has a much broader field than surgical analgesia. Moreover, the chapter written by the medical profession on the elimination of intractable and nonsurgical pain lacks brilliance. Therapy that includes narcotics with depression of bodily function and eventual addiction or the radical and often mutilating surgical interventions as satisfactory remedies leaves much to be desired. Any substitute that promises to exempt bodily pain for even a relatively small number of sufferers has merit. Particularly is this true of therapeutic nerve blocking, since in competent hands it does not add to the patient's discomfort except temporarily in some cases during the manipulation and is not often followed by untoward reactions. It has the further advantage of noninterference with other forms of treatment and requires minimal or no hospitalization. Moreover, therapeutic nerve blocking recently has won a commanding argument for more general recognition, since it has proved of value not only for relief of pain but to arrest the whole process of certain disturbed physiologic mechanisms and bring about a return to normal.

The foregoing statements should not be construed as a recommendation for the indiscriminate or widespread use of nerve blocking. They are a plea for a more generous appreciation of its advantages, for more energetic efforts to explore its possibilities, to

master and develop its technics and assign it to its proper place in therapy.

The number of nerve blocks that have been reported, often enthusiastically, in medical literature comprise an imposing list. It would be presumptuous to say that all these should assume a definite place in therapy. Experiences with the great majority of those recommended have not been extensive nor have the procedures stood the test of uniformly successful results. However, many therapeutic nerve-blocking procedures have been employed widely, and sufficient data have accumulated to insist that they merit further trial and more widespread application. Some of these have been employed at the New York University-Bellevue Medical Center with optimistic results.

Organization for Nerve Blocking

Hospitals generally are adequately organized and equipped to manage nerve-block procedures that are required for surgical anesthesia. Spinal, caudal and local anesthesia is done in most institutions by the department of anesthesia or the surgeon with dispatch and satisfactory results, and in many institutions certain simple regional procedures such as brachial plexus, lumbar sympathetic and other nerve blocks are regularly completed. There are comparatively few institutions where an organized service is maintained for therapeutic and diagnostic nerve blocking. In an institution such as Bellevue where more than 800 of these procedures are completed each year and where graduate and postgraduate teaching is in constant progress, such an organized service is mandatory.

An operating room used exclusively by the service is essential, and adjoining it a workroom where the nurses in charge of the clinic prepare materials such as solutions, syringes and needles and the many other accessories required, when not assisting the operator to do nerve blocks or assuming immediate care of patients. The operating room must be provided with temperature control and have adequate teaching equipment such as skeletons, charts and diagnostic instruments. Provision must be made for any emergency treatment needed. Patients are received from the hospital wards by appointment and from outpatient clinics and the admitting ward at any time. Records are the responsibility of the Anesthesia Department.

It was planned early that the Nerve Block Clinic would be a location where the technical procedures could be completed. Patients were to come from other services with a diagnosis and with the kind of block desired indicated. This plan was soon abandoned, because often the combined efforts of several specialists are needed to reach even a tentative diagnosis—the psychiatrist, neurologist and orthopedist often, as well as others.

If progress is to be made, the emphasis should be not on technics but rather on a search for better understanding of pain mechanisms and the reaction patterns to different pain syndromes. More clinical experiments are indicated, and results need to be scrutinized more critically.

Therapeutic Nerve Blocking in Clinical Practice

In clinical practice today, therapeutic nerve blocking has come to mean the injection of anesthetic or neurolytic solutions into painful areas or contracted muscles or along the course of segmental or autonomic nerves. When single injections are used to anesthetize nerve endings around torn ligaments or broken bones or in painful muscles or joints, only temporary relief is required and elaborate technics are not needed. The inflicted painful area is found with the needle and the anesthetic solution is deposited. The procedure is repeated as often as required until it is no longer needed. These blocks may be done as office procedures for ambulant patients. Injections at trigger points can be carried out similarly to attack pain syndromes less obvious than a sprained ankle or a broken rib. They may seek to aid in a condition of prolonged duration.

Over the years, indications for nerve blocking as a means of treating disease have gradually increased. Recently, application of this approach has extended to include important conditions previously carrying a high mortal-

ity [illegible] Space does not permit even a listing of [illegible] indications, which have been the subject [illegible] extensive reference works.[1,2] It serves a practical purpose to classify pain syndromes and evaluate each nerve block according to the existing pathologic process.

Classification of the Pain Syndrome

Although pain is a term difficult to define, its etiologic factors make it possible to provide a rational classification. The most extensive causes of pain are the result of organic changes in the visceral and neuromusculoskeletal systems. These include trauma, infection, neoplasms and many similar conditions. Frequently these conditions are self-limited and require only temporary pain relief. It is in these circumstances that nerve blocking finds the most widespread but not its most important application. When these conditions become chronic, the usefulness of nerve blocking is given its greatest challenge and its most disappointing results.

Pain classed as neurologic in origin includes those syndromes designated as neuritis or neuralgia. These are differentiated by the evidence that in neuralgia histologic changes cannot be found.

A third group of conditions causing pain are associated with spasm of smooth muscle, particularly in the digestive, urinary and circulatory systems, especially the latter. Here nerve blocking of the appropriate autonomic pathways has been especially effective not only in controlling pain but also in aiding diagnosis and treatment of the underlying pathologic process.

Finally, the nature of certain pain experiences makes it difficult to classify pain except on a psychogenic basis with no etiologic factor in evidence. Those who have had considerable experience with nerve blocking will recall many subjects in this category who have received unexplained relief from nerve blocks which have no established indication.

It is a constant observation that the more significant nerve blocks having therapeutic value are those which eliminate undesirable reflexes arising as the result of trauma or disease. Such reflexes may result in spasm of skeletal muscle, which may be treated by segmental nerve block or local infiltration. Neuromusculoskeletal conditions such as pain involving joints and post-traumatic conditions with painful sequelae are treated similarly. Vascular conditions, vasomotor disturbances and vasospasm are treated by appropriate blocks of pathways of the autonomic nervous system.

No group of patients with pain as a predominant symptom are more difficult to treat than those with carcinoma. In the large majority this pain is difficult to localize and relieve with nerve blocking. However, the results are gratifying to many patients. If the nerve supply to the growth is determined and is accessible, as is frequently the case in malignancies of the face and neck, nerve blocks are definitely indicated. When the new growth involves abdominal viscera, the pain pathways may not be interrupted easily. Blocking segmental nerves alone is not often sufficient, and autonomic fibers must also be paralyzed. If some type of physiologic nerve section can be devised to obviate recourse to progressively increasing and ineffectual morphine medication or the serious chordotomy, it should be done. Certainly an effort to apply such procedures should precede the initiation of addiction or radical neurosurgery. Epidural injections, and in some extreme cases subdural injections, may be indicated. Neurolytic solutions (alcohol, phenol) have been used successfully in these circumstances.

Summary

The early history of nerve block is reviewed to outline the development of this practice, which led to one of its more recent ramifications, therapeutic nerve blocking. The present status of analgesic and neurolytic injections in the therapy of pain and disturbed physiologic processes is briefly discussed.

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Practical Physiologic Therapy in Metabolic and Electrolyte Imbalances

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DISTURBANCES of body water content, electrolyte composition, or acid-base balance result from (1) unusual stress on essentially normal body mechanisms, (2) functional impairment of organs responsible for maintaining the chemical environment of the body, or a combination of these two broad etiologic categories. Representative of the first category are patients without cardiopulmonary, hepatic or renal disease who require postoperative intestinal intubation and in whom inappropriate replacement therapy leads to loss of gastrointestinal secretions and development of a metabolic disturbance. Common clinical examples of the second category are patients who have acute or chronic cardiac, hepatic, renal or pulmonary disease which progresses to the point of "decompensation."

"Routine fluid orders" do not constitute optimal or practical therapy any more than would routine orders for digitalization or diuretic programs. Treatment of any electrolyte imbalance requires a "metabolic prescription" in terms of the amounts of all the components to be administered per 24 hours, each constituent considered independently of all the others.

A concept of practical value in terms of prognosis, evaluation of therapy, and organization of treatment is that which analyzes disease syndromes according to the existing functional capacity and the load relationships of all parts of the body (load/capacity ratio).

The physiologic basis for the clinician's word "decompensation" deserves emphasis. A physician observing a patient free of symptoms actually classifies him as "compensated"; all organs of the body are able to reach a functional capacity necessary to perform their tasks. As a useful clinical concept, "compensation" is a situation in which the load (the stress or physiologic task) of an organ is less than its functional capacity. The load/capacity

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ratio is less than 1.0. "Decompensation" may be viewed as a situation in which the total demand on a particular organ is greater than that organ's functional capacity, i.e., the load/capacity ratio is greater than 1.0. Some of the major physiologic tasks should be noted.

1. The cardiocirculatory system must maintain a cardiac output appropriate for all levels of activity, maintain pressure and flow in arterial, capillary and venous circulations within normal limits, and meet peripheral tissue demands for perfusion.

2. The lungs must add oxygen to and remove carbon dioxide from blood in amounts which meet requirements for the existing energy expenditure. This requires the "bellows function" of the lungs to exchange air in the alveoli with an efficiency appropriate for all levels of alveolar ventilation, an alveolar-capillary membrane normally permeable to carbon dioxide and oxygen (i.e., freedom from alveolar-capillary "block"), suitable distribution of pulmonary capillaries so that all ventilated alveoli are adequately perfused, and a normal total pulmonary blood flow.

3. The kidney must manipulate excretion of electrolytes and water (essentially independent of one another) and thereby maintain normal composition and amounts of body fluids. This also involves excretion of the usual "acid load" of the diet without loss of an equivalent amount of body base ("base conservation" function of kidney).

Many forms of disease may be analyzed as a disturbance of the load/capacity ratio, and this concept is of genuine practical value. In terms of prognosis, as well as predicting efficacy of therapy, it is often as important in the extremely ill patient to evaluate changes in load versus alterations in functional capacity as it is to establish a specific etiologic diagnosis. It facilitates organization of clinical treatment for the purpose of reducing load (the total stress on the patient) or improving the functional capacity of the organ primarily involved by disease.

Chemical Environment of the Body

It may be said that our present concepts began with Claude Bernard,[1] the famous French physiologist, who in 1857 provided a theory which has proved to be one of the most useful in human physiology. Bernard perceived that all cells of the body were bathed in a fluid which varied very slightly in terms of temperature, composition and alkalinity. This constancy of the internal environment, in which the cells exist, contrasts sharply with the variability of the external environment, in which the total organism, the aggregate of all the cells, exists. Intermittent intake of water, electrolytes, protein and calories in highly variable amounts is countered by integrated mechanisms designed to maintain this stable internal chemical environment. The most important conceptual elements of this physiologic integration can be presented by an oversimplified and schematic diagram, which is illustrated in figure 1.

The cells are bathed by interstitial fluid which is in active exchange with the intracellular contents as well as the intravascular contents, by virtue of specific permeability relationships of cell membranes and capillary membranes. Appropriate to the metabolic needs of the cells in the different tissues, materials leave the blood by passage through the capillary membrane, traverse the interstitial fluid, and enter the cells across the cellular membrane. The metabolic end products of cellular activity move in opposite directions and return to the blood from the cells. In addition to this exchange of nutrients and removal of metabolic products (taking place in all tissues of the body), the blood serves as a circulating medium to all organ systems, permitting specialized exchanges as required by the organ's role in the maintenance of the internal environment. Thus, removal of particular materials from or their addition to the blood maintains plasma, interstitial fluid and intracellular water at a constant composition.

The "cells" in the diagram in figure 1 represent not only those of the organs with specialized functions in the control of the internal environment but also the skeletal muscle cells, which form the greatest bulk of cellular mass in the body. Skeletal muscle is approximately 70 per cent water, as are the other cells of the body except those of bone and adipose tissue.

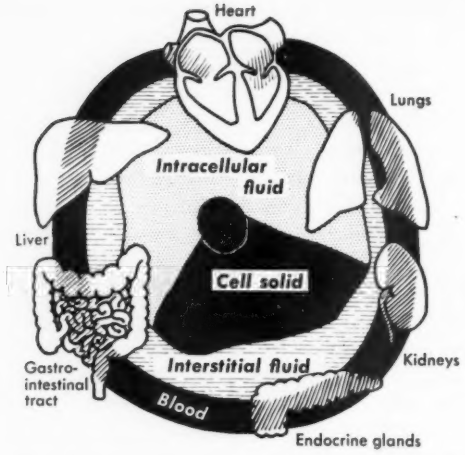

FIGURE 1. Schematic diagram illustrating Claude Bernard's theory of the internal environment of the body. The cells of the body exist in the interstitial fluid rather than in the external environment. For explanation, see text.

The solid is largely protein. In an adult man weighing 70 kg. or 154 lb., total body water is approximately 60 per cent of body weight (45 l.).[2] Some 33 l. of this is intracellular water.[3] Plasma volume is approximately 4 per cent of body weight (3 l.), and interstitial fluid volume 12 per cent (9 l.).[4] These percentages change, since adipose tissue is a variable component of total body weight in normal persons, and, because human fat contains little water, increasing fat content reduces the previously noted values, expressed as fractions of total body weight.* The values do, however, provide a useful idea of the volume relationships of intracellular water, interstitial fluid and plasma volume (figure 2).

The chemical anatomy of these compartments of body water has been defined (figure 3). Plasma and interstitial fluid are quite similar in composition except for protein content. This restriction of plasma protein within the vascular volume plays an important role in normal plasma-interstitial fluid exchange. Although slight protein leakage occurs in all capillaries, the skeletal muscle capillaries are much less permeable to protein than are the capillaries of the liver or intestinal tract.

Sodium is the most important cation (base) in extracellular fluid. Potassium, calcium and magnesium are other cations present in much smaller amounts. Chloride and bicarbonate form the largest portion of the anions (acids), with smaller amounts of phosphate, organic acids and protein. For several reasons, amounts of these ions are expressed in milliequivalents per liter, and therefore the sums of cation and anion columns are equal.*

Intracellular fluid composition is in obvious contrast. Potassium and magnesium are the major cations; phosphates, sulfate and protein are the major anions. Small amounts of the other electrolytes are present in varied amounts in different tissues.

There are slight differences in the concentration of electrolytes in plasma and interstitial fluid. These differences are a result of the restriction of protein to the vascular compartment and are satisfactorily explained by the theory of Fredrick Donnan.[7] *Metabolic activity is not involved in the maintenance of these small differences in concentration.* How-

*The water content of human adipose tissue is related to the interstitial fluid and connective tissue contained therein.

*The milliequivalent is a measure of chemical "combining ability" while the milligram is a measure of chemical weight. One milligram of sodium does not combine with 1 mg. of chloride, or with 1 mg. of any other element, but 1 mEq. of sodium will combine with 1 mEq. of chloride, or 1 mEq. of any other element of opposite electric charge. One milliequivalent is related to one electric charge, whether positive or negative, and therefore, expressed as milliequivalents, the total number of positively charged elements is equal to the total number of negatively charged elements in terms of their chemical "combining ability." This is a form of chemical bookkeeping which indicates that in body fluids positively charged ions must be balanced by an equivalent number of negatively charged ions in order to have the observed electric neutrality. Another form of chemical bookkeeping in body fluids requires that the osmotic concentration be essentially equal in the cells, interstitial fluid and plasma. Osmotic concentration is an expression of the *number* of particles in solution without reference to electric charge. Salt (NaCl) in water dissociates almost completely to sodium ions (Na^+) and chloride ions (Cl^-) with greater osmotic activity of the salt solution than predicted from NaCl concentration. Sodium or potassium bound to negative charges in cell protein dissociates less than the base in plasma. This explains the higher total concentration of elements within the cell as compared with interstitial fluid (figure 2), since with less dissociation greater concentration is necessary for equal osmotic activity.

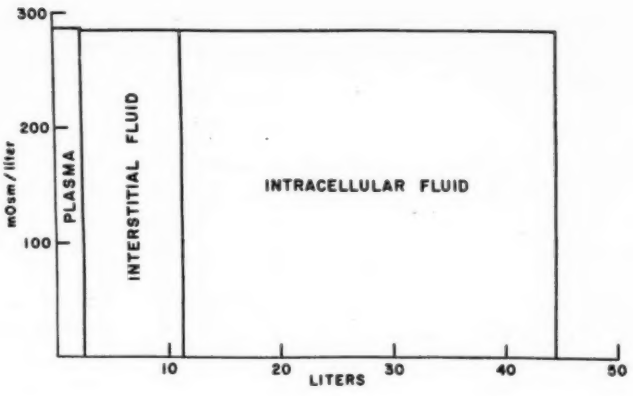

FIGURE 2. Relative volumes of the main body water compartments: plasma, interstitial fluid and intracellular fluid. Note that osmotic concentration is essentially equal within the three compartments except for the minimal difference in plasma tonicity accounted for by the oncotic pressure of plasma proteins.

(Modified from Marriott.[5])

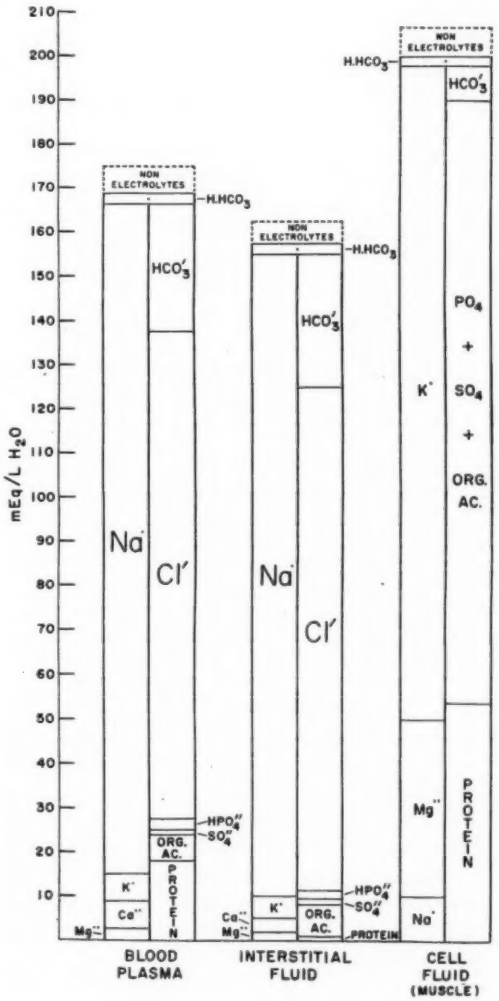

FIGURE 3. Chemical anatomy of plasma, interstitial fluid and intracellular fluid.

(From Gamble.[6])

ever, the difference in electrolyte composition of extracellular versus intracellular fluid cannot be explained in terms of the Donnan theory or any physicochemical law and reflects the metabolic activity of cells. These observed differences in concentration are considered a result of active transport of potassium into the cell (concentration of potassium within the cell) and of active transport of sodium out of the cell (at a rate appropriate to maintain the reduced intracellular sodium concentration).

If the cell is supplied with adequate nourishment (calories from carbohydrate or fat sources, important extrinsic enzymes such as vitamins, insulin, and so on), and with proper amounts of its constituents (amino acids for protein synthesis, water, electrolytes, particularly potassium and magnesium), its own activity will govern and provide a normal intracellular environment.

The composition of interstitial fluid is predictable from the composition of plasma, taking into specific consideration the varied permeability to protein in the capillaries of the different organs.

Plasma composition is a conjoint responsibility of the lungs, kidneys and liver. By virtue of its role in albumin synthesis, the level of plasma protein may reflect liver function. Pulmonary function determines the amount of carbon dioxide gas dissolved in the blood and

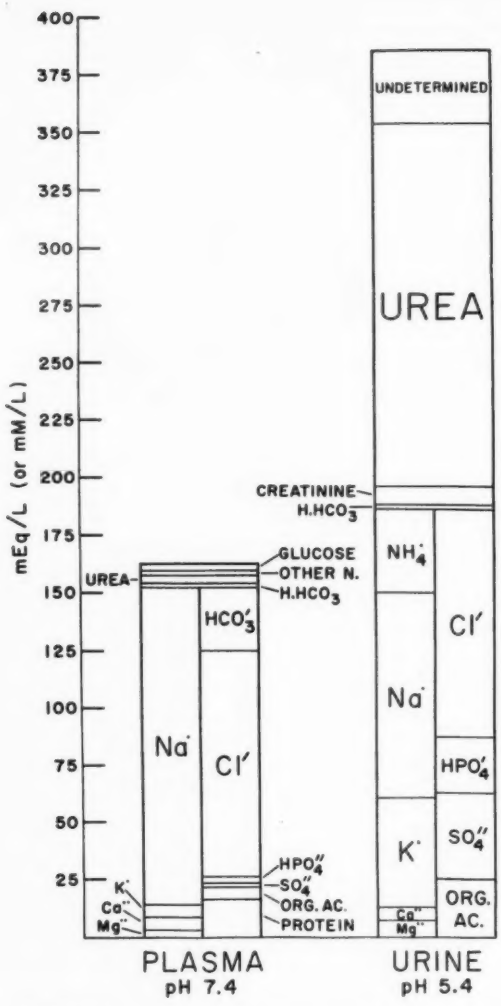

FIGURE 4. Comparison of the composition of normal plasma and an "average" 24 hour urine sample.

(From Gamble.[6])

consequently the amount of the hydrated form of the gas, H_2CO_3, in the plasma. Increased dissolved carbon dioxide in the plasma, as a result of impaired pulmonary function, will tend to produce respiratory acidosis. Hyperventilation with subsequent reduction in dissolved carbon dioxide leads to respiratory alkalosis. All other constituents of the plasma are under the control of the kidneys.

The complex mechanisms by which the human nephron accomplishes multiple tasks have been reviewed in detail,[8,9] and it is unnecessary to restate them here to provide some clinical understanding of the role of normal renal function in the maintenance of the chemical environment of the body.

Excess intake of any constituent of the body normally under renal control will result in increased urinary excretion. Conversely, restricted intake will be countered by a reduction in urinary excretion, if renal function is normal. The rate at which the normal kidney can compensate for an alteration in intake varies with different materials. Excess ingestion of water results in a prompt polyuria of a dilute urine. Excess intake of salt may produce transient weight gain, since the adaptation for increased sodium excretion is less rapid. In similar manner, the body inventory of all materials under renal control is kept within normal range.

The average American diet provides adequate calories, a protein content varying from 50 to 150 gm. a day, from 6 to 11 gm. of salt (100 to 200 mEq. sodium), 1.5 to 3.5 gm. of potassium (40 to 80 mEq.), and smaller amounts of other electrolytes noted in the diagram. Since an "average" 24 hour urine volume is approximately 1200 cc., total fluid intake (water ingested plus water formed by metabolic oxidation) amounts to 1500 to 2500 cc. a day, the difference accounted for by loss of water through the lungs, skin and colon.

These items pose no significant burden in terms of normal renal function. Indeed, the major requirements of renal function under conditions of ingestion of a normal diet may be perceived from an examination of the composition of an "average 24 hour urine sample" (figure 4). In comparison with the plasma, the increased concentrations of phosphate, sulfate and organic acids are apparent, as well as the increase in nonelectrolyte (mainly urea). The phosphate and sulfate are derived from metabolism of protein and fat.* Urea is derived

*Approximately 60 mEq. of sulfate and 50 mEq. of phosphate are produced from 100 gm. of protein, and 50 mEq. of phosphate from 100 gm. of fat containing 10 per cent lecithin. Phosphate or sulfate derived from catabolism of body protein or fat does not differ from that produced by metabolic oxidation of these constituents in the diet.

from protein metabolism by virtue of deamination of amino acids in the liver. Excretion of this amount of phosphate and sulfate (i.e., "acid load") without loss of "body base" (mainly sodium) is accomplished by acidifying the urine and replacing a portion of base by ammonium ion generated within the renal tubule.* This "base conservation" function of the kidney is of major importance in the maintenance of the internal environment and is frequently affected in renal disease.

The load on this "base conservation" mechanism may increase markedly under circumstances of high intake of protein and fat, starvation with increased endogenous protein breakdown as well as mobilization of fat stores, or the common clinical situation of poor calorie intake combined with the acute metabolic response to injury or illness. Catabolism is prominent with acute illness or injury, and increased amounts of phosphate and sulfate are delivered to the renal mechanism for excretion. In patients with impaired renal function (reduced capacity), increased load may result in sodium depletion due to impaired sodium conservation as well as varying degrees of phosphate and sulfate accumulation and acidosis. The hazard of the catabolic phase in illness, injury and surgery and postoperatively in patients with chronic renal impairment may be explained to a significant degree in these terms.

The extremely variable composition of normal urine reflects (1) a "base conservation" mechanism which functions as determined by the "acid load" of the diet, (2) a volume of urine such as to maintain body water content within normal limits, and (3) an adjusted electrolyte excretion determined by the difference between electrolyte intake and body requirement for each ion.

Normally, persons select *ad lib.* a metabolic prescription (table 1) similar qualitatively but extremely variable in regard to the amounts of various constituents. The latter variation reflects individual and ethnic preferences in food, beverages and flavorings.

*The important contribution of the urinary buffers in base conservation cannot be discussed adequately here; for details, see Smith.[9]

TABLE 1

THE DAILY "METABOLIC PRESCRIPTION"*

1. Volume of water
2. Total calories
3. Protein
4. Vitamins
5. Potassium
6. Sodium
7. Chloride
8. Other electrolytes

*Components of total oral intake which healthy persons select *ad lib.* These components must be appropriately adjusted in all patients with metabolic imbalances.

General Principles of Therapy

Treatment of any electrolyte disturbance requires the physician to order all components of this "metabolic prescription" for his patient *in terms of the amounts to be administered per 24 hours, without emphasizing one item.* The responsibility remains of making sure this administration is *completed* in 24 hours. The amount of each constituent is evaluated from the patient's clinical state and is considered essentially independently of all the others. When this evaluation is completed, the 24 hour intake of each can be administered by combining appropriate amounts of parenteral fluids.* Formulas for the amounts of the individual materials to be administered should *not* be employed, since these are approximations at best; they do not take into proper account the influence of mixed electrolyte abnormalities, they often are too complicated for their limited accuracy to justify memorization, and they fail to meet the need for individualization of therapy, a requirement which is particularly urgent in the patient with metabolic imbalance.

Individualization of rational therapy is an essential characteristic of modern medical practice. Modes of administration of digitalis, diuretic therapy and antibiotic dosage are illustrative of areas in which the experienced clinician manipulates therapeutic agents in a manner which will afford the most subtle bene-

*Nine-tenths per cent saline contains 154 mEq. sodium and 154 mEq. chloride per liter. Sixth-molar sodium lactate contains 156 mEq. sodium per liter.

TABLE 2

SAMPLE 24 HOUR METABOLIC PRESCRIPTION*

Continuous infusions:

1. 1000 cc. 10 per cent glucose in water with 20 mEq. potassium chloride, vitamins
2. 500 cc. 10 per cent glucose plus 200 cc. 0.9 per cent saline and 300 cc. sixth-molar sodium lactate
3. 1000 cc. 10 per cent glucose in water with 20 mEq. potassium chloride

Rate of infusions: 1000 cc. per eight hours (approximately 35 drops per minute)

Totals:

Volume 3000 cc.
Calories 1000
Protein 0
Sodium 81 mEq.
Potassium 40 mEq.
Chloride 71 mEq.

*An illustrative "average metabolic prescription" provided from available parenteral fluids. From this base line, modifications are made for treatment in particular clinical disturbances as discussed in the text.

fits to the patient. This principle is equally important in the treatment of metabolic imbalances. Routine application of equations or "routine fluid orders" do not constitute optimal (or practical) therapy any more than would routine orders for digitalization or diuretic programs.

In practical terms and from information available at the bedside, including commonly performed laboratory studies, how can this be accomplished? Individual treatment of any clinical disturbance may be devised by modification of any *reasonable* "average metabolic prescription."

As an illustration, let us maintain on intravenous fluids a healthy adult. In excellent metabolic balance, this normal adult allows considerable latitude in his "average metabolic prescription" (table 2). Obviously this does *not* supply all that his previous oral intake contained, but it does provide enough to attenuate markedly the undesirable effects of complete cessation of oral intake. The moderate amount of exogenous nonprotein calories (250 gm. carbohydrate equals 1000 calories) tends to reduce endogenous protein breakdown, thereby limiting negative nitrogen balance as well as the acid load for excretion. Total water content is adequate for extrarenal needs and for 24 hour urine volume, without requiring maximum urinary concentration. The major electrolytes are present in moderate amounts, and thus neither excessive excretion nor excessive conservation by the renal apparatus is required. Negative balances of nitrogen and calories are not marked and are well tolerated under conditions of normal nutrition.

It has been demonstrated that the load of phosphate and sulfate required for renal excretion may be reduced to a minimum value, determined by the patient's clinical state, by administration of a forced, high calorie diet with no protein, since protein-sparing action is greatest with this program.[10] In the absence of various pathologic causes of tissue breakdown, endogenous protein metabolism may be reduced to an order of 20 to 30 gm. per day.[11] The 100 gm. of glucose (400 calories) usually employed in intravenous fluid orders serves to prevent starvation ketosis from undue fat metabolism and exerts a significant protein-sparing effect,[12] but protein catabolism is significantly greater than it is on an adequate or abundant carbohydrate-calorie intake. The need for maximum protein-sparing effect is urgent in patients with renal disease, as exemplified in the development of the no-protein, forced-calorie programs of Borst,[13] Bull and associates[14] and Kolff[10] for the treatment of "lower nephron nephrosis."

In order to obtain the caloric benefit of intravenous glucose, glycosuria must be avoided, and therefore the intravenous fluids must be distributed throughout the 24 hour period. This is done by specifying continuous infusions with a defined rate of infusion (drops per minute or cubic centimeters per hour) and by stating the hour at which the infusions should be completed.

Intravenous fat emulsions will play an increasingly important role in supplying caloric needs as preparations become entirely acceptable for routine clinical use. For the present, intravenous carbohydrate is used as the source of calories in most hospitals.

Before the infusion of fluid is completed, the attending physician evaluates the clinical state of the patient, reviews new laboratory

data, revises the "metabolic prescription" if indicated, and arranges the plan for the next 24 hours of therapy.

It should be emphasized that it is preferable to infuse glucose over 24 hours whether the total volume of water to be administered in that interval is small or large. For example, in the case of a patient with anuria due to acute renal failure who is unable to maintain oral intake, the total 24 hour water requirement is of the order of 750 cc., although daily caloric requirements often are increased. Two hundred and fifty grams of glucose would be administered in 750 cc. of water (33⅓ per cent glucose, 500 cc. of 50 per cent glucose diluted to 750 cc.); the 750 cc. of glucose solution is infused at a rate of approximately 30 cc. per hour. These extremely hypertonic solutions are not employed as a matter of choice, but are given only if required by the clinical situation. If they are infused slowly, as recommended, the sole undesirable side effect may be thrombophlebitis at the site of the infusion. One can minimize this possibility by placing a small amount of heparin (5 to 10 mg. per liter of intravenous fluid) in the infusions. This apparently serves to reduce the effects of local irritation. (Heparin would not be employed in the presence of any coagulation defect.) The hazard of significant caloric deficits in the poor-risk patient is greater than that of peripheral thrombophlebitis.

Protein as protein hydrolysate, human salt-poor albumin or plasma proteins (from aged, hepatitis virus-free plasma) may be added to the "metabolic prescription" as indicated. Protein *cannot* be used for tissue synthesis unless adequate calories from other sources are present in the daily allotment. Patients who are maintained for lengthy periods on parenteral feedings require some form of protein supplementation. An essential aspect in preventing protein malnutrition is provision of exogenous calories so that body protein will not be catabolized for caloric requirements.[15]

Some Therapeutic References in Specific Clinical Situations

The modifications to be made in this basic prescription are evident in many clinical situations. In the immediate postoperative period, when sodium excretion is negligible (if renal function is normal), sodium should be eliminated from the prescription unless intestinal fluid loss is continuing or dehydration is present. Conversely, potassium excretion will tend to rise, and in the presence of adequate renal function potassium may be administered throughout the postoperative interval.

The presence of dehydration of any cause requires an increased daily allotment of water. This additional fluid will be retained in the extracellular compartment if additional sodium is administered. In dehydration of acute onset, although sodium and water deficits can be extreme, intracellular potassium may not be greatly affected. If dehydration develops more chronically, reduction in extracellular sodium is accompanied by a decrease in intracellular potassium, in which case the daily prescription should include increased amounts of potassium. However, if plasma potassium concentration is normal, potassium should *not* be given until the low urinary volume seen with severe dehydration begins to increase with administration of intravenous fluids.

When renal function is normal, and appropriate amounts of sodium and potassium are supplied each 24 hours, the 24 hour urine volume may serve as one clinical guide to the adequacy of total fluid administration. When the 24 hour urine volume reaches 1500 cc., one may assume that dehydration has been corrected and may reduce the total fluid administration to a maintenance level.

The necessity for sodium restriction in the edematous patient is well documented and the practice widely followed. However, equal attention should be directed to all elements of the "metabolic prescription." Accrued caloric deficit and loss of protein tissue are common in persons with chronic cardiac, hepatic or renal disease because of anorexia or restricted diets. This solid-tissue wasting may operate as a secondary complicating feature of the basic pathologic process, diminishing response to therapy and thereby perpetuating the major problem in a vicious clinical cycle. Increased secretion of aldosterone occurs in nephrotic, hepatic and cardiac syndromes, and

a potassium deficit may develop in these edematous patients, particularly during vigorous diuretic therapy. This should be treated by increased potassium intake.

In advanced congestive heart-failure or portal cirrhosis with ascites it is not uncommon to find a plasma sodium level substantially below normal limits ("dilutional hyponatremia"). This represents not so much a deficiency of sodium as it does an excess of water in the body, although our understanding of the genesis of this problem is inadequate. In the absence of clinical symptoms indicative of "low sodium syndrome" no attempt should be made to increase this low plasma sodium concentration by administration of hypertonic saline. It is quite true that in this era of vigorous sodium-depletion therapy a "low sodium syndrome" may be superimposed on "dilutional hyponatremia" (and thus sodium would be indicated in treatment), but this represents a complex and special case which cannot be discussed adequately here.

Medical practice confronts the physician with many dilemmas. One is the patient who presents a combination of azotemia, acidosis, dehydration and varying distortions of electrolyte concentrations. This clinical combination may be observed to follow an injury, a surgical procedure, a gastrointestinal disturbance accompanied by vomiting and diarrhea, or an acute infection of some severity with consequent inadequate oral intake. It is essential in planning therapy to estimate the possible contribution of intrinsic renal disease to the observed azotemia, acidosis and oliguria.

When dehydration exists, gradual correction of the sodium and water deficit will result in increasing urine volumes. Therefore, at least a maintenance amount of water and sodium should be given in the first 24 hours. If urine flow does not increase as dehydration is corrected, one may surmise that intrinsic renal functional impairment is present and must consider this in devising the "metabolic prescription." Correction of dehydration provides useful information regarding the existing clinical function of the kidneys and is indicated even in acute renal failure.

This picture often has a predominantly prerenal component, and gratifying clinical improvement often occurs as adequate calories, water, sodium and other electrolytes are administered. If this is not the case, significant functional impairment of an organ which contributes to the maintenance of the chemical environment of the body probably exists, and requires special evaluation and management.

When edema exists in conjunction with acidosis, azotemia and an essentially normal plasma sodium concentration, sodium is restricted, water is provided in low maintenance amounts, and attention is directed to meeting daily caloric needs with carbohydrate. Advanced intrinsic renal functional impairment with limitation in the 24 hour urine volume is the most common cause of this clinical picture.

Estimation of appropriate amounts of sodium versus chloride to be administered is an additional aspect of this problem. A practical point of origin is the concentration which exists in the plasma: Plasma sodium is 140 mEq. per liter, plasma chloride 100 mEq. per liter. Therefore, if the sodium-chloride ratio is 140 to 100, or 1.4 to 1, no harm can be done since patients who are acidotic will tend to become more normal and those who are alkalotic will also become more normal. Practically, this balance of sodium and chloride in the "metabolic prescription" is achieved by using varying amounts of 0.9 per cent sodium chloride and sixth-molar sodium lactate (or sodium bicarbonate). With an obviously greater need for sodium than for chloride, or vice versa, the proportions are adjusted accordingly. In hypochloremic alkalosis due to pyloric obstruction, only 0.9 per cent sodium chloride could be employed, as the proportion of sodium to chloride (156 mEq. to 156 mEq.) would replace chloride more rapidly than sodium. (Normal renal adjustment would eliminate excess sodium.) Intravenous ammonium chloride should rarely be employed. For sodium depletion and acidosis following diarrhea, sodium lactate solution would be combined with saline, and the proportion of sodium to chloride 150 mEq. to 50 mEq. might be a reasonable estimate for the first 24 hours of therapy; it may be modified as the clinical course indicates.

Conclusion

This discussion is designed to serve as no more than an introduction to a complex subject. It is a subject of great practical significance to physicians. With an aging population we are now entering an era in which associated disease of independent etiology commonly occurs, producing a clinical picture which is atypical and requiring treatment based on evaluation of organ function impairment. For example, the treatment of respiratory acidosis in a patient with chronic lung disease who also has chronic renal disease involves more than therapy of the pulmonary problem and is complicated by the existence of the renal lesion.

With the remarkable growth of information in the general field of human metabolism, more than a few physicians have become particularly concerned with problems of the chemical environment of the body. In most instances interest has been focused on renal and electrolyte problems. It would be well to resist any tendency to be concerned with one organ in the body, despite the interest in detailed study of intimate aspects of renal function. One should be as much concerned with the cardiocirculatory system as with the plasma sodium concentration; should worry no more about glomerular filtration rate than about adrenal, hepatic and thyroid function; pay no more concern to the proximal convoluted tubule and the loop of Henle than to ventilatory-perfusion relationships of lung alveoli, or factors influencing formation of osteoid tissue and its subsequent calcification. If the clinician maintains an approach which analyzes disease syndromes as abnormal steady states fixed at levels determined by existing functional capacity and load relationships of all parts of the body, his consultation and advice will be of practical help in treating complex disturbances of the internal environment.

Enhanced understanding of all the disturbances of physiologic mechanisms which comprise the picture of disease in the individual patient does not guarantee clinical improvement, but it does provide the only rational framework for treatment which can be expected to yield the best attainable result in that situation.

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Some Clinical Aspects of Complete Heart Block

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There are several cardiac mechanisms associated with Adams-Stokes syncope, and their separation has therapeutic implications. Treatment of the acute syncopal attack and the prevention of recurrences are outlined. Ephedrine sulfate and isopropylarterenol are the most widely used pharmacologic agents. Various instruments which function as external pacemakers have been developed, and use of such devices ultimately may be the preferred treatment.

HERBERT J. KAYDEN

Of the cardiac problems associated with disorders of rhythm, complete heart block is one of the most interesting. Both in diagnosis and in management, it can be relatively simple or extremely complex. This discussion covers some clinical features and indicates some of the technics for managing the problems that may arise.

The normal transmission of the cardiac impulse from the atria to the ventricles is via the atrioventricular node, a band of specially differentiated tissue extending from the lower portion of the interatrial septum near the opening of the coronary sinus to the membranous portion of the interventricular septum. Conduction is slower through the atrioventricular node than in other areas of the heart. When the time for conduction of the cardiac impulse from atria to ventricles exceeds the normal limits, the disturbance is called prolonged atrioventricular conduction or first-degree heart block. Occasional failure of conduction has been classified as partial or second-degree heart block. Complete or third-degree heart block refers to the cardiac mechanism when the contractions of the atria and of the ventricles are controlled by independent pacemakers. Although complete atrioventricular dissociation may occur with a ventricular rate that is more rapid than the atrial rate (due to dissociation by interference or ventricular capture), the more common form of complete dissociation is manifested by a ventricular rate

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that is much slower and independent of the atrial rate. This rhythmic disturbance is referred to as complete heart block.

Clinical Types

Although the majority of cases of complete heart block are associated with arteriosclerotic heart disease, this abnormal rhythm has been noted in many other cardiac conditions.

Congenital complete heart block has been diagnosed during pregnancy by the unusually slow fetal heart rate. Most such infants have an associated structural defect of the heart, usually an interventricular septal defect, but this abnormality may be difficult to demonstrate. In other infants, abnormal communications between the left and right sides of the heart cannot be found and no other anomaly can be discovered. It has been suggested that in these cases there is a fibrous structure separating the atrioventricular node from the common bundle of His. In the absence of congenital cardiac malformation, these children grow and develop normally, and the cardiomegaly that develops is usually well tolerated.[1]

Development of complete heart block has been recorded during the course of many acute infectious diseases. Until recently, diphtheria was a frequent cause. Complete heart block during the acute phase of rheumatic fever is not common, although prolongations of the PR interval frequently develop.

Complete heart block may be an incidental finding in routine examination of middle-aged persons, but in elderly patients the arrhythmia is usually symptomatic. It is the elderly group which comprises the greatest number of patients, and the ensuing discussion is devoted to a consideration of problems that may arise in these cases and methods of managing them.

Palpitation may be the first symptom of a disordered rhythm. It is uncommon for the patient to be aware of a slow rate if the heart rate is more than 40 beats per minute, but he may be conscious of the slow, forceful pulse when the rate is in the 20s.

A significant proportion of the total cases of complete heart block develop during the first days of an acute myocardial infarction, particularly infarction involving the posterior wall. The abnormal rhythm may be noted simply by the change in rate, by the form of the electrocardiogram, or by the appearance of Adams-Stokes syncope. Appearance of this arrhythmia during the course of acute myocardial infarction has been reported to be a grave prognostic sign. However, if the patient survives the acute episode of infarction, electrocardiographic studies have shown that the complete heart block is almost always temporary and the prognosis for life is no worse than that of the myocardial infarction and the heart disease itself. It has been suggested that complete heart block developing with myocardial infarction is produced by an inflammatory reaction extending toward the atrioventricular node, and that edema and pressure, rather than actual destruction of the nervous pathways, cause the interference with conduction. The fact that corticosteroids sometimes abruptly revert the aberrant rhythm to a normal atrioventricular conduction pattern supports this concept.

One of the most dramatic clinical states associated with complete heart block is Adams-Stokes syncope. An excellent clinical description of the syncope and convulsions was detailed more than 200 years ago, but the electrocardiographic classification was made barely 25 years ago. Individual episodes vary greatly in severity and duration from brief syncope to a frankly epileptiform convulsive state lasting several minutes and followed by a long period of drowsiness and confusion. Clinical observations during the syncopal or epileptiform state have suggested the presence of cardiac asystole because of absence of heart sounds and of peripheral pulsations, but frequent electrocardiograms have revealed that ventricular standstill by itself probably is the cause of Adams-Stokes syncope in less than half the cases.[2] Ventricular tachycardia followed by standstill, and ventricular tachycardia followed by ventricular fibrillation with or without subsequent standstill (figures 1 and 2) are the other important rhythmic abnormalities responsible for the syncopal attacks. The therapeutic implications of this separation of cardiac mechanisms will be discussed subsequently.

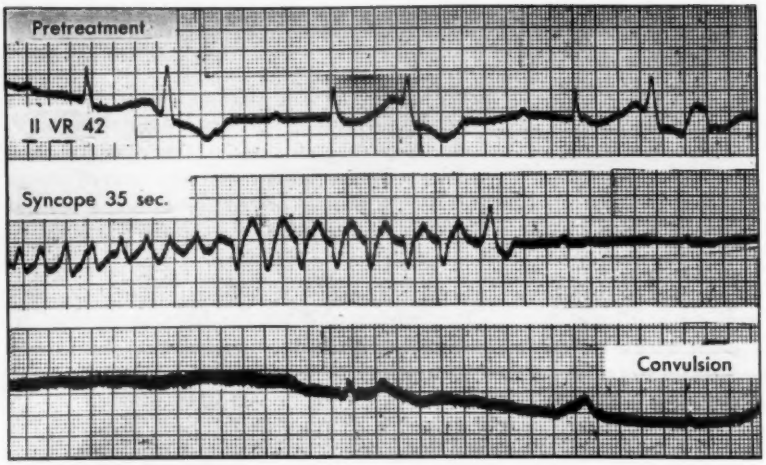

FIGURE 1. Electrocardiogram of Adams-Stokes syndrome due to ventricular fibrillation and ventricular arrest. Ventricular premature systoles are seen in the upper lead.

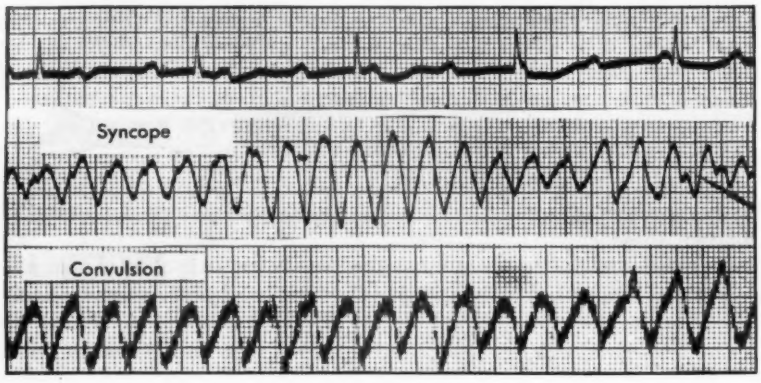

FIGURE 2. Electrocardiogram of Adams-Stokes syndrome due to ventricular fibrillation.

Diagnosis

The diagnosis of complete heart block should come to mind in any case of marked bradycardia. The rate is generally regular and between 30 and 40 beats per minute. A striking auscultatory variation in the intensity of the first heart sound at the apex is almost pathognomonic of complete heart block; in some cycles the sound is muffled, in others it is of average intensity, and in some it is very loud. A second auscultatory finding is atrial sounds due to atrial contractions during long diastolic intervals, sounds best heard between the apex and the edge of the sternum and more distinct early in diastole than in the latter part. Careful observation of the jugular pulse may also reveal atrial contraction waves during the long diastolic pause. None of these findings are present if the atrial rhythm is fibrillation rather than normal sinus rhythm.

The electrocardiograph is the diagnostic clinical tool in confirming the presence of complete heart block. The atrial and ventricular complexes are unrelated throughout the electrocardiographic tracing. The form of the QRS complex may be either normal or abnormal depending on the site of the idioventricular pacemaker.[3]

In recent years, several studies have been made involving physiologic measurements of hemodynamic function in patients with complete heart block in the presence and absence of congestive heart-failure.[4] In the absence of congestive heart-failure, patients with complete heart block usually demonstrated elevated pressures in the right side of the heart, increased systolic and pulse pressures in systemic arteries, increased systemic and pulmonic vascular resistance, and reduced cardiac output despite an increased stroke volume. Two other abnormalities usually found in pa-

tients with congestive heart-failure have been observed in these patients, namely, increased arteriovenous oxygen difference and impaired renal hemodynamic function with an elevated filtration fraction. Although these physiologic measurements suggest congestive heart-failure, these patients have been followed for a number of years without the clinical manifestations of congestive heart-failure. The data obtained by cardiac catheterization in patients with complete heart block and the clinical finding of congestive heart-failure show an accentuation of the abnormalities observed in patients in the noncongested state. Some of these abnormalities are reversed by the intravenous administration of the sympathomimetic amine isopropylarterenol.

In some patients, there is an interval prior to the establishment of complete heart block when fainting spells of short duration occur. After one of these episodes the patient may appear entirely normal and the electrocardiogram shows little or no evidence of conduction defect. These cases may be misdiagnosed as major or minor epilepsy, hysteria or other disease entities. Sometimes the physician cannot establish the nature of the syncopal attack until he actually observes one. Carotid sinus stimulation may reproduce the attack and the electrocardiogram may show the alteration, transiently, to complete heart block with ventricular asystole.

Treatment of Complete Heart Block

The management of the patient with a static slow rate who has few symptoms and no syncopal attacks is comparatively simple. Specific medication usually is not required, although ephedrine sulfate, 0.024 gm. three times a day, frequently is given, or a 10 mg. GLOSSET® of isopropylarterenol (ISUPREL®) four times a day. Fortunately, these patients comprise the large majority of cases of complete heart block. Their management is not difficult, and the prognosis is that of the underlying heart disease.

The situation is quite different for patients with complete heart block who are subject to syncopal attacks. Because the frequency of the attacks varies from minutes to months or years, it is difficult to outline a treatment schedule. Further, treatment to prevent attacks which occur every few minutes may be very complex, in contrast to a program to prevent recurrences months or years apart, which may be far simpler. For 200 years it has been observed that some patients with complete heart block have phases in their clinical course when many Adams-Stokes attacks occur and then have freedom from such episodes for months or even years. No satisfactory explanation for the periodicity of these attacks is available.

Before undertaking treatment of the syncopal attack, it is imperative to ascertain the precise physiologic disturbance present. As already noted, there are two basic cardiac mechanisms that may be present during the attack: (1) a sudden ventricular arrest not preceded by ventricular irritability and (2) a period of frequent ventricular extrasystoles or ventricular tachycardia which culminates in ventricular flutter or fibrillation and may then be followed by a period of cardiac arrest. Precise differentiation can be made only by electrocardiography, but frequent auscultation may reveal long pauses in cases in which the first-named mechanism is present, and the irregularity of the heart beat due to ventricular extrasystoles in the second group (figure 1). The need for frequent examination and careful observation of the patient with recurrent syncopal attacks makes it necessary in most cases to transfer the patient to a hospital.

In treatment of the acute attack, the sympathomimetic amines are the most useful medical agents for stimulating and maintaining the rhythmicity of the heart. Epinephrine, isopropylarterenol (Isuprel) and ephedrine are the three most potent agents which affect cardiac rhythm. Epinephrine must be administered parenterally, either subcutaneously (0.5 ml. of a 1 to 1000 solution) or intramuscularly in oil (0.5 to 1 ml. of a 1 to 500 solution), or as a constant intravenous infusion. We have felt that the margin between the therapeutic and toxic doses of isopropylarterenol is wider than that of epinephrine, and that isopropylarterenol is therefore more suitable for management of acute episodes. It is administered subcutaneously, 0.2 mg. every 40 to 60 minutes,

or as a constant intravenous infusion at the rate of 1 to 8 μg. per minute. Intravenous infusion requires constant electrocardiographic monitoring, and indeed the electrocardiograph is essential for the management of all patients with frequent Adams-Stokes syncope. It has been our observation that the sympathomimetic agents are useful in both forms of syncope. In cases of sudden ventricular arrest, the drugs maintain the idioventricular pacemaker and prevent sudden cessation of ventricular beating. In the cases of ventricular tachycardia, flutter and fibrillation, they appear to be effective by maintaining the usual idioventricular pacemaker at a sufficiently rapid rate so that ectopic centers cannot build up and discharge as a dominant focus.[5]

In the light of these observations, it becomes apparent why both procaine amide (PRONESTYL®) and quinidine are contraindicated and dangerous for patients with complete heart block. It would appear that the idioventricular pacemaker is exquisitely sensitive to the depressant action of these two agents; as the normal rate is slowed, aberrant rhythms develop with disastrous consequences.

A number of electric devices have been developed to serve as external cardiac pacemakers.[6] These have adjustments to regulate both the rate and the force of the stimulus. Various other electronic instruments may be added which automatically start the electric pacemaker whenever the interval between successive heart beats exceeds a prescribed time. These instruments are very useful during the unstable period when a patient is having many attacks of Adams-Stokes syncope day and night, and they are constantly being improved and reduced in size. Part of the impetus for development of these instruments stems from the production of complete heart block during the surgical repair of certain congenital cardiac defects. Intracardiac electrodes implanted directly or via an antecubital vein and attached to external pacemakers are now available at certain medical centers, and use of such devices may ultimately be the preferred treatment.

Many other medications have been recommended for treatment of complete heart block with or without Adams-Stokes syncope. Intravenous molar sodium lactate has been recommended, but its action appears erratic and frequently ineffective. The adrenal steroids have been used, and except for a possible beneficial effect in patients in whom complete heart block develops during the early days of myocardial infarction they have not been effective.

Maintenance therapy to prevent recurrence of syncopal attacks involves careful clinical observation, for requirements vary in each case. Different schedules with changes both in frequency of administration and in amount of each dose must be tried to achieve optimal results. Ephedrine sulfate and isopropylarterenol are the two most useful orally administered agents for the long-term management of complete heart block at the present time.

Summary

Some of the clinical features of complete heart block are reviewed. There are several cardiac mechanisms associated with Adams-Stokes syncope, including ventricular tachycardia followed by standstill, ventricular tachycardia followed by ventricular fibrillation, and cardiac asystole. Therapeutic regimens for the acute syncopal episode as well as to prevent recurrent attacks are outlined. Ephedrine sulfate and isopropylarterenol are the two most widely used pharmacologic agents.

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Natural History of the Nephrotic Syndrome in Glomerulonephritis

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It is not known whether the histologic renal changes in the nephrotic syndrome represent sequelae of classic acute glomerulonephritis or whether the nephrotic and nonnephrotic types of glomerulonephritis are different diseases. A tentative conclusion is reached, based on correlation of histologic and clinical observations in 22 cases, that the condition as defined herein is not a sequela of classic acute glomerulonephritis but a separate disease. The probable sequence of structural glomerular changes is described.

THE nephrotic syndrome, when not related to another disease such as diabetes mellitus, disseminated lupus erythematosus or amyloidosis, is generally considered to be a stage in the course of glomerulonephritis. Classically it is described as the intermediate or degenerative phase of glomerulonephritis, occurring some time after the latent period which follows the initial acute stage. It is stated that the nephrotic syndrome subsides after months or years as the hypertensive and uremic stage of glomerulonephritis supervenes. According to this view, the end stage of the disease in patients who have passed through a nephrotic phase is indistinguishable both clinically and pathologically from the terminal picture in those who have never been observed with the nephrotic syndrome. It is also believed that in both groups of patients the course starts with acute glomerulonephritis, which may go unnoticed in some of them, and that in those patients who fail to recover from the initial acute glomerulonephritis the nephrotic syndrome does not always develop at an intermediate stage of their disease.[1]

Other observers have felt that from both clinical and pathologic evidence glomerulonephritis may represent a different disease in patients who manifest the nephrotic syndrome than it does in those who do not. They have stressed the fact that the nephrotic syndrome

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appears insidiously and have expressed the view that it is unreasonable to assume that an initial episode of acute glomerulonephritis almost invariably goes unnoticed in such patients. These observers have further emphasized the almost uniformly poor prognosis of the nephrotic syndrome in glomerulonephritis. These considerations, together with certain pathologic findings which appeared to be distinctive, led Ellis[2] to classify glomerulonephritis into types 1 and 2, representing essentially the non-nephrotic and nephrotic types, respectively. The implication of the Ellis classification is that these two types of glomerulonephritis are distinct diseases etiologically and pathogenically.

Our understanding of the natural history of the nephrotic syndrome in glomerulonephritis has been enhanced during the past three years by the correlation of findings of serial renal biopsy and of necropsy with observations on clinical course and renal function. The discussion which follows represents an interpretation of our findings in 22 cases studied in this manner.

Definition of the Nephrotic Syndrome

We define the nephrotic syndrome as renal loss of albumin resulting in diminished serum concentration, variably associated with hyperlipoidemia and edema. Renal loss of protein is considered the primary defect; the other manifestations are secondary, influenced by the various extrarenal factors affecting the metabolism of protein, lipids, salt and water. This has led to a definition of the nephrotic syndrome by Berman and Schreiner[3] based solely on a 24 hour excretion of protein exceeding 3.5 gm., since patients with the complete syndrome usually excrete more than this amount. Our objective in defining the nephrotic syndrome is to enable us to select a group of patients in whom we may determine whether this clinical state correlates with a particular anatomic and clinical sequence of events, possibly with therapeutic implications. If we require the presence of the complete syndrome, as conventionally defined, we may erroneously exclude certain patients because of variability in the secondary manifestations. On the other hand, if the definition depends solely on the quantity of protein excreted, we are forced to accept an arbitrary minimal value for this and, further, may find ourselves including patients in whom protein excretion exceeds this amount only transiently. We believe our definition is useful, because it surmounts these objections by requiring that the extent of protein excretion be sufficient to depress serum albumin. We consider the serum albumin concentration reduced when it is less than 3 gm. per 100 ml.

Natural History of Structural Changes

Although the evolution of structural glomerular changes in patients with the nephrotic syndrome in glomerulonephritis has not been thoroughly documented by serial renal biopsies, we shall describe what we consider the probable sequence of events.

In most of our patients whose kidneys were examined pathologically before evidence of renal insufficiency, glomerular abnormalities apparent on light microscopy consisted of mild to moderate irregular or fairly uniform thickening of the capillary basement membranes (membranous glomerulonephritis*) (figure 1a) or focal hyaline nodular change in many glomeruli (lobular glomerulonephritis*) (figure 2; see also figure 6). These two abnormalities often are seen together and may be variants of the same process. The exact nature of the eosinophilic material which accumulates in glomeruli is not known. It has many of the

*The terms "membranous glomerulonephritis" and "lobular glomerulonephritis" are purely descriptive diagnoses and do not imply that the etiologic or pathogenic factors are the same in all cases.

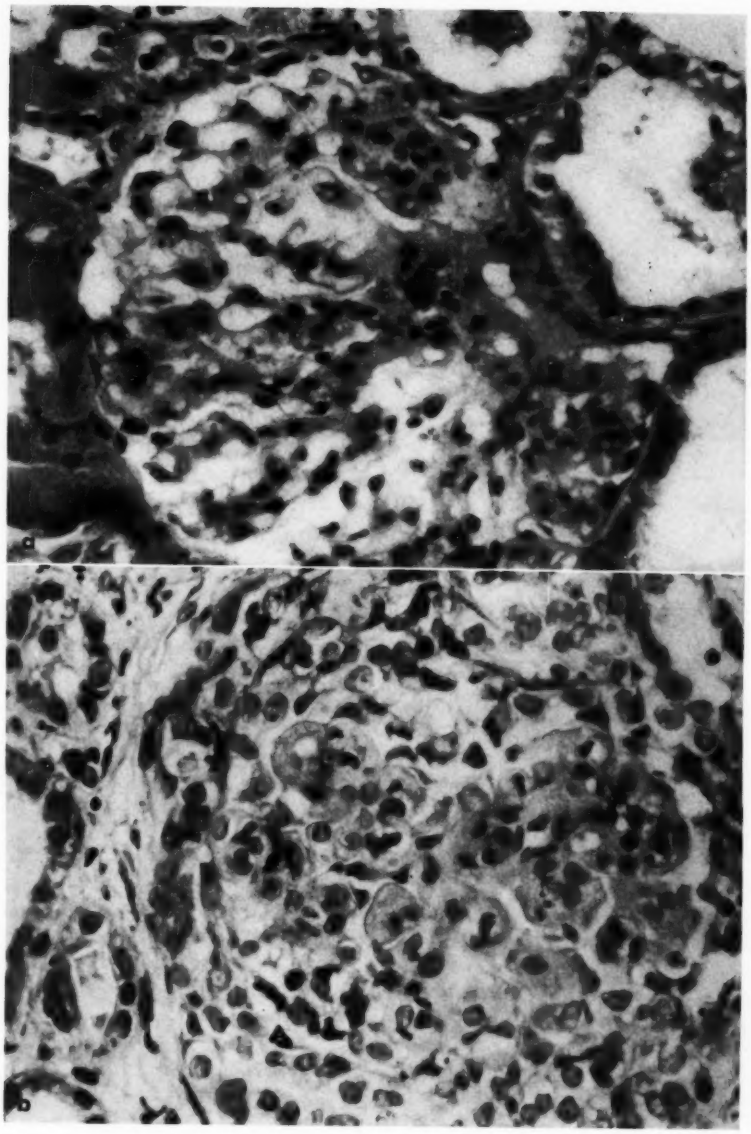


FIGURE 1a. Photomicrograph of renal biopsy specimen. 15 year old white girl, 13 months after the appearance of the nephrotic syndrome. Hematuria at onset. Normal blood pressure and renal function at time of biopsy. No response to adrenal steroids. Glomeruli showed a mild and irregular accumulation of eosinophilic material. Hematoxylin-eosin, x 300.

b. Renal biopsy 20 months after the first biopsy and one month after appearance of rapidly progressive renal failure and hypertension with persistence of the nephrotic syndrome. Patient died two months later with uremia. Glomeruli showed marked membranous changes and epithelial crescents. Hematoxylin-eosin. x 300.

staining properties of collagen. Electron microscopic studies have been reported in a few cases of chronic glomerulonephritis as showing increase in basement membranelike material.[4] Whatever its nature, it appears to represent a reaction to injury comparable to scar tissue formation in other locations.

In a few of our patients in whom biopsy was performed early in their disease, there were virtually no glomerular abnormalities apparent on light microscopy (figure 3). Similar cases have been studied by others with the electron microscope and have been reported to show loss of the epithelial foot processes or defects in the basement membrane.[4,5] It is possible that these patients represent exam-

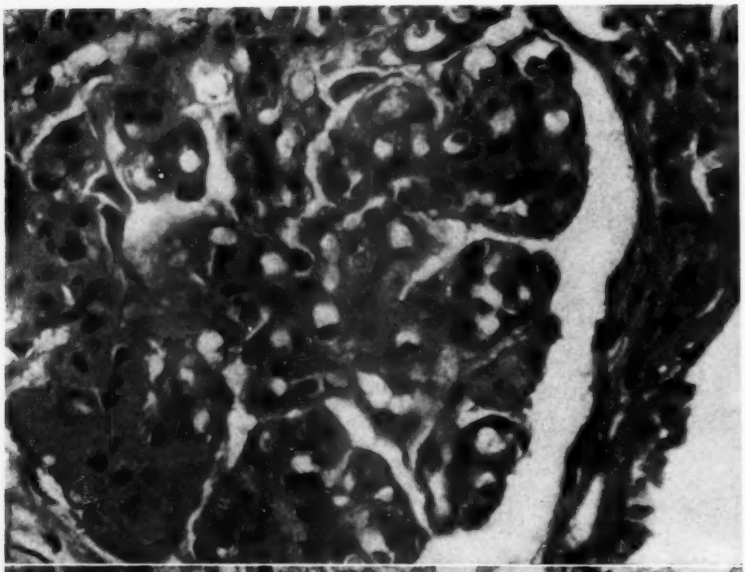


FIGURE 2. Renal biopsy, 43 year old Chinese man, four years after appearance of the nephrotic syndrome. Normal blood pressure and moderate impairment of renal function. No response to adrenal steroids. Glomeruli showed marked membranous and lobular change. Hematoxylin-eosin, x 300.

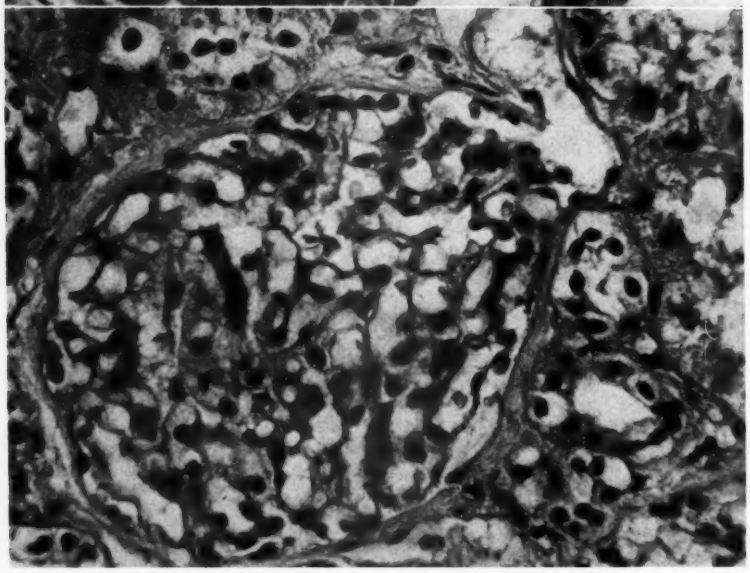


FIGURE 3. Renal biopsy, 17 year old Negro girl, 21 months after the insidious appearance of the nephrotic syndrome with normal blood pressure and maintenance of normal renal function. Remission induced with adrenal steroids. No definite abnormalities in the glomeruli. Hematoxylin-eosin, x 300.

ples of a separate disease (lipid nephrosis) from which recovery is the rule. On the other hand, patients with the nephrotic syndrome whose kidneys appear normal pathologically may very well represent the earliest stage of membranous or lobular nephritis; this transition has not been demonstrated by serial renal biopsies, nor has the transition from pathologically proved acute glomerulonephritis to membranous nephritis with the nephrotic syndrome. In other words, the initial pathologic changes of membranous or lobular nephritis are not known.

In patients dying from uremia, the kidneys usually showed very marked membranous or lobular glomerulonephritis. The glomeruli were

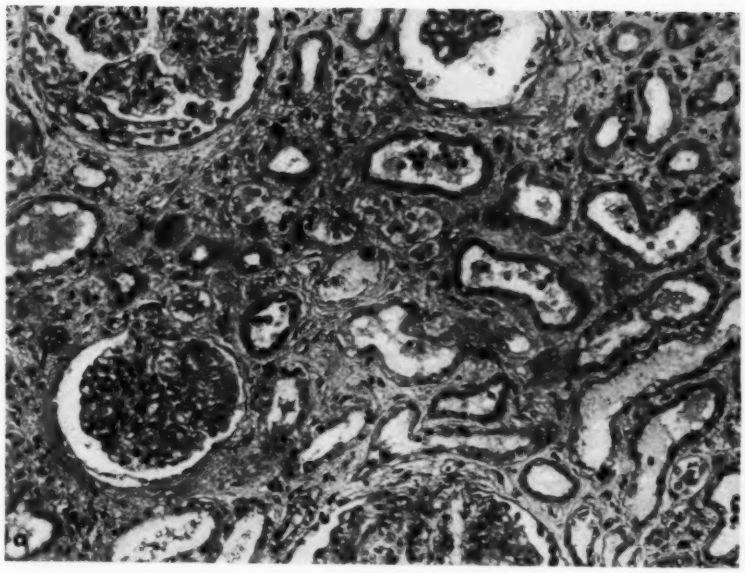
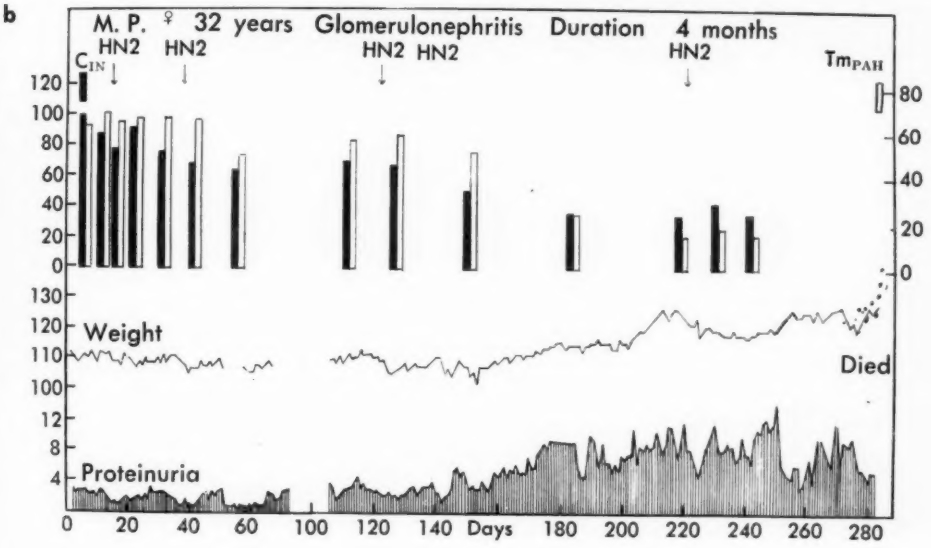


FIGURE 4a. Photomicrograph of renal section obtained at necropsy, 32 year old white woman who died 14 months after the insidious appearance of the nephrotic syndrome. Progressive renal failure from onset with persistence of the nephrotic syndrome. Glomeruli showed moderate membranous change and crescents. Moderate uniform interstitial fibrosis. Hematoxylin-eosin, x 100.

b. Chart of patient's course. Progressive diminution of glomerular filtration rate and maximal tubular excretory capacity (Tm_{PAH}) with increasing edema and proteinuria is shown.



involved to a fairly uniform extent; there was little disappearance of glomeruli, with only mild, rather diffuse interstitial fibrosis (figure 4). In contrast, the kidneys of patients dying with glomerulonephritis in which the nephrotic syndrome had not been part of the clinical course characteristically showed considerable atrophy, disappearance of many glomeruli with the remaining glomeruli showing irregular hyalinization or hypertrophy, and usually conspicuous arterial and arteriolar sclerosis (figure 5). It must be stated, however, that differentiation between these two forms cannot always be made pathologically. An additional feature which was seen in most of the patients in our series was the presence of

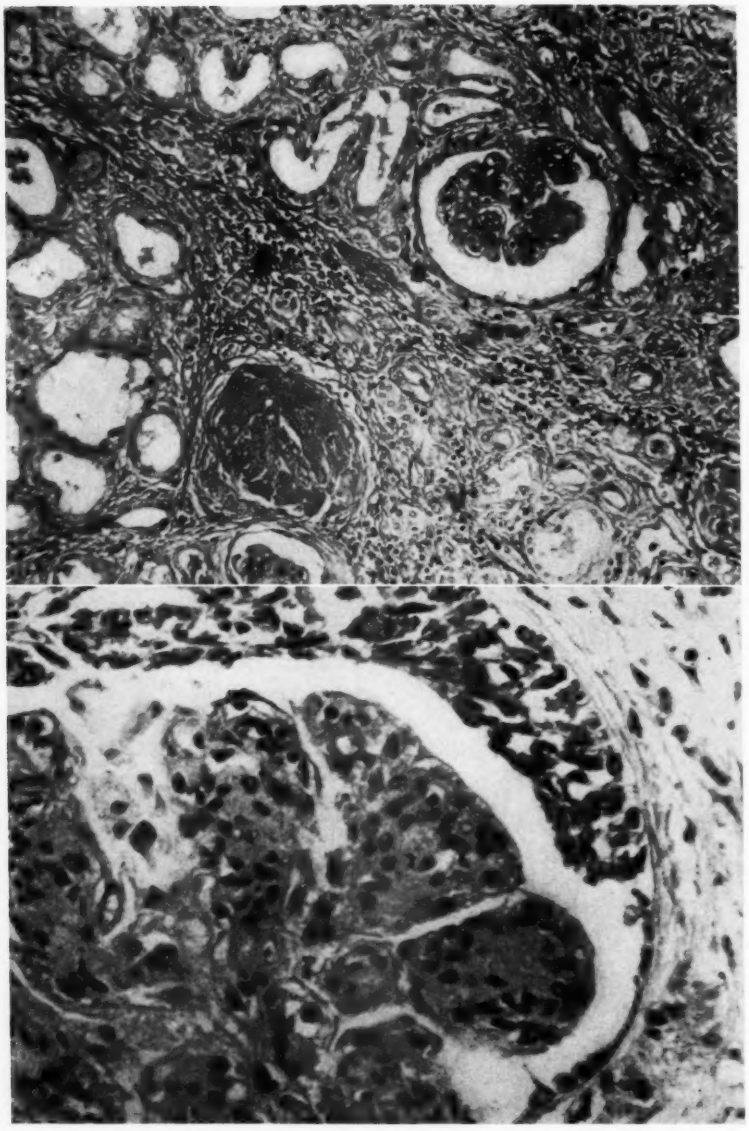


FIGURE 5. Section of kidney showing the features generally considered to represent the end stage of chronic glomerulonephritis that follows classic acute glomerulonephritis. There is uneven involvement of glomeruli with hyalinization of some, and irregular interstitial fibrosis with areas of atrophy and hypertrophy of tubules. Hematoxylin-eosin, x 100.

FIGURE 6. Section of kidney obtained at necropsy, 28 year old white woman first observed with the nephrotic syndrome, hypertension and renal functional impairment nine months after insidious onset. Patient died with uremia two years after onset with persistence of the nephrotic syndrome. Glomeruli showed marked lobular and membranous change, and there were numerous crescents. Masson trichrome, x 300.

numerous epithelial crescents at the end stage of the disease. In one patient it was possible to observe by serial renal biopsies the transition from a picture of pure, rather mild membranous alteration to a picture of severe membranous change with numerous epithelial crescents in addition (figure 1a and b).

In several other patients in whom there was a long history of the nephrotic syndrome followed by uremia leading to death, a similar pathologic picture was found and it seems likely that the crescents developed after a long period of membranous change (figures 4 and 6). The development of numerous epithelial crescents undoubtedly is important in intensifying renal insufficiency. Such cases may be

diagnosed as "subacute" by the pathologist, but they appear to represent an entirely different process from that seen in patients with fairly rapidly progressive renal insufficiency developing from the initial acute stage of glomerulonephritis and leading to death in weeks or months. In these patients, the pathologic picture often differs in showing more intense acute inflammatory reaction in glomeruli and less severe and widespread membrane thickening, although if the process continues long enough it is associated with diminution in the inflammatory reaction and increasing membranous change; so it is impossible on pathologic grounds alone to differentiate it from the process in which crescents develop after a long period of membranous changes.

In summary, the sequence of events in patients with the nephrotic syndrome in glomerulonephritis seems to consist of minimal structural glomerular alterations initially, followed by progressive accumulation of eosinophilic material either diffusely in capillary walls or in the form of nodules, in many cases to be accompanied in the later stages by the appearance of numerous epithelial crescents. At no stage is there conspicuous inflammation in glomeruli.

Natural History of the Clinical Course

The onset of glomerulonephritis in most of our patients (14 of 22) in whom the nephrotic syndrome developed subsequently was characterized by some features of acute glomerulonephritis; i.e., antecedent infection, transient elevation of blood pressure, hematuria or renal insufficiency was observed frequently. We do not have renal biopsy findings for this stage. However, in patients whose onset was "acute" in this sense the nephrotic syndrome developed during or directly following this phase, and rarely (four times) was there an interval before its appearance. When there was an interval, it was characterized by persistence of some of the initial manifestations and would not be described as a latent stage in which proteinuria is the only abnormality. When the nephrotic syndrome did not appear or follow closely after these "acute" manifestations, the mode of onset was in the form of insidious appearance of edema. Renal biopsies later in the disease showed similar pathologic alterations whether the disease had begun acutely or insidiously.

In the majority of patients, renal function at the time of appearance of the nephrotic syndrome was not impaired significantly, except in some of those whose disease appeared to start acutely. When impairment was present at the onset, it usually was transient, and improvement toward normal function followed and persisted for a time (with occasional recurrence of transient impairment) before the progressive and terminal decline in function which occurred eventually in most. In one case, a renal biopsy during a phase of transient and marked functional impairment showed no glomerular abnormalities. Rarely, impairment of renal function found at the time of first observation during the nephrotic syndrome did not remit but progressed to the time of death. Renal biopsy in three such patients showed moderate or far-advanced glomerular damage, and we surmise that the disease had been present for some time before our first observations were made or had progressed rapidly in a short time.

In general, it may be stated that impairment of renal function at the time of onset is transient and that patients with the nephrotic syndrome typically are observed initially and for some time thereafter with essentially normal function. Pathologically these patients typically show rather mild membranous or lobular nephritis (figure 1a).

The same general statements may be made concerning elevation of blood pressure. Transient elevation may be present at the onset, and in rare instances hypertension may persist throughout the course, but usually there is normal blood pressure during the course of the nephrotic syndrome and hypertension appears toward the end in conjunction with renal insufficiency.

Remission of the nephrotic syndrome, either spontaneous or induced, occurred after many months or years in about one-fifth of our patients, leaving them with normal function and blood pressure and little or no proteinuria. In four such cases, renal biopsies during remis-

sion showed either normal glomeruli or minimal basement membrane thickening (figure 3). These patients may relapse (we have seen one relapse after 12 years), but in some the urine persistently is free of protein and it may be concluded after one year of such complete remission that a patient has recovered from the disease. The possibility that this group of patients have a different entity, i.e., lipid nephrosis, must be considered (and this interpretation is strengthened by the finding of normal or minimally altered glomeruli in such cases), but we believe that this diagnosis can be considered fruitfully only in retrospect, as there is no way to predict the course of nephrotic patients from the clinical manifestations at the onset.

In the great majority of our patients with the nephrotic syndrome, progressive renal insufficiency and hypertension eventually developed, and death usually occurred within three years of the onset. The duration of the disease from onset to the time of death varied, however, and was as short as five or six months and as long as five or six years. Most of the patients continued having massive proteinuria and hypoproteinemia to the end, and only rarely did we observe a subsidence of the nephrotic manifestations during the terminal period of hypertension and uremia. The transition from the phase of normotension and maintained normal renal function to the stage of hypertension and renal failure usually was rather abrupt, and the disease moved rapidly to the end in months once there was evidence of progressive renal failure. It was during this phase that epithelial crescents appeared in addition to progressive membranous or lobular changes in some cases (figures 1b, 4 and 6), and it seems likely that this superimposition of epithelial proliferation plays a role in the acceleration of renal insufficiency. In those patients whose period of progressive renal impairment was slower and prolonged to two to three years, the nephrotic features subsided toward the end. When this occurred, the glomeruli were largely obliterated and the membranous features were no longer apparent.

Remission with adrenocorticosteroids could be induced in about half our patients. Response to steroids is of prognostic significance, as all our patients whose disease eventually remitted for long periods or who maintained normal blood pressure and renal function for several years responded favorably to steroids. On the other hand, a number of patients responded to steroids only to enter later the phase of progressive renal impairment, failing at that time to respond favorably. As a rule, those with evidence of advancing disease failed to remit with steroids, although others who apparently were not progressing, as evidenced by maintenance of normal renal function and blood pressure, also showed no tendency to remit with steroid therapy. We have concluded that ability to induce remission with steroids may indicate a favorable prognosis, but not necessarily so, whereas failure to induce a remission with steroids usually suggests a poor prognosis. Renal biopsies showed that all of the patients who responded to steroid therapy had only minimal glomerular abnormalities, whereas with one exception the patients who failed to respond had moderate or severe glomerular changes. We are not yet able to assess the effect of steroids on the outcome of the disease, and it is doubtful if a definitive answer to this question can be obtained readily in view of the highly variable course. It is of interest that in our series the incidence of spontaneous remission and of steroid-induced "permanent" remission was the same (approximately one of five patients).

Summary and Conclusions

Histologic findings in the kidneys of patients with the nephrotic syndrome, when it is not related to a known disease such as diabetes mellitus or disseminated lupus erythematosus, consist of progressive accumulation of eosinophilic material which may vary in distribution within glomeruli, followed in many cases by the appearance of epithelial crescents. These findings are correlated with maintenance of essentially normal renal function for a period usually not exceeding two or three years and with the subsequent development of progressive renal failure. Pathologists refer to the histologic changes as chronic glomerulonephritis, but it is not known whether they

represent, in fact, the sequelae of classic acute glomerulonephritis. Some observers believe that the late histologic findings in patients whose chronic renal disease follows acute glomerulonephritis differ from those in patients whose disease is characterized by the nephrotic syndrome. Others do not accept the validity of separating chronic glomerulonephritis into two pathologic types, but in any case an attempt to classify glomerulonephritis on the basis of necropsy material is difficult in that far-advanced glomerular changes may give no evidence as to origin or mode of development. Inasmuch as the glomerulus, like other structures, can respond to injury in only a limited number of ways, varying types of damage may result eventually in similar histologic lesions.

Obviously, a satisfactory classification of glomerulonephritis into one or several separate diseases would be arrived at best by identification of the etiologic or pathogenic factors involved. Lacking this, we believe correlation of serial renal biopsies with the clinical course may yield valuable information relative to the nature of glomerulonephritis, as the sequence in which structural changes occur may be more revealing than the character of the process at any one time.

On the basis of what we have observed, we incline to the view that patients with the nephrotic syndrome such as we have discussed do not have a condition which is a sequela of classic acute glomerulonephritis but rather that they have a separate disease. Our conclusion is tentative, however, and more observations are needed at the onset in patients in whom the nephrotic syndrome eventually develops and in the intermediate stages in patients in whom chronic disease develops following acute glomerulonephritis.

The question whether the nephrotic syndrome with virtually no glomerular abnormalities represents still another disease entity, lipid nephrosis, also is unsettled.

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Nutritional Disturbances Associated With Diabetes Mellitus

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The nutritional disturbances associated with diabetes mellitus have been controlled to a considerable extent by the use of insulin, but the nature of the disease is such that normal metabolic pathways may be interrupted readily, with a breakdown in utilization of the major foodstuffs.

The diabetic diet should supply the substances for which the demand is increased, and should contain liberal amounts of qualitatively adequate protein. Dietary supplementation with essential nutrients, such as the various vitamin fractions, is important. The diet should be as reasonable as is consistent with good care. Calorie intake should be adjusted to age and occupation.

ELAINE P. RALLI

METABOLIC diseases, involving as they do the metabolism of the major foodstuffs, are often associated with nutritional disturbances. This is particularly true in diabetes mellitus, where both the disease and its dietary treatment may contribute to the nutritional situation. If one goes back into the history of diabetes one finds descriptions of symptoms and physical findings indicating that nutritional abnormalities were quite common. In the preinsulin era, when the diabetic patient's diet was restricted in many essential nutrients, peripheral neuritis was a common complication of the disease—so common, in fact, it was referred to as diabetic neuritis.[1] Today, with the administration of vitamin B_1[2] and use of a more liberal diet, this complication has practically disappeared.

The principal nutritional disorders in diabetes are due to abnormalities in metabolism of protein or fat, to deficiencies or disturbances in metabolism of many of the vitamins

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or their precursors, and to the disturbances in electrolyte balance.

Disturbances in Protein Metabolism

At present the diet of the patient with diabetes usually is fairly adequate in its protein content. However, there still is a tendency to restrict the total protein intake. The diet should be liberal in qualitatively adequate protein. Approximately 70 gm. in the form of meat, fish, milk and milk products should be allowed, especially for the diabetic child, as the period of growth requires additional protein. Evidence of protein deficiency often is not interpreted as such. For example, the enlarged fatty liver which is present in many diabetic children at some time during their period of active growth is undoubtedly due to a relative deficiency in protein. This can be controlled by increasing the protein intake and by administering vitamin B_{12}, which has a lipotropic effect.[3]

Several factors increase the sensitivity of the liver to damage in diabetes. The carbohydrate disturbance affects the liver's capacity to store glycogen, and when the liver is depleted of glycogen it is more susceptible to damage. Hypoglycemia, which may occur in the diabetic person receiving insulin, stimulates the secretion of epinephrine and there is a consequent breakdown of liver glycogen to blood sugar.[4]

Recent experimental work suggests that the quantity of protein in the diet is related to the activity of a number of the enzyme systems in the liver. In a person with uncontrolled diabetes or on a poorly balanced diet, energy is supplied to a large extent from the metabolism of fatty acids. This tends to lead to the development of a fatty liver and points up the importance of including adequate amounts of protein in the diet.

Another evidence of protein malnutrition in patients with diabetes is the abnormality observed in the serum electrophoretic pattern.[5] In the young diabetic there is a tendency for a decrease in the serum albumin level, which is lower than in young normal subjects, and in the distribution of the globulin fractions, the alpha globulin being higher and the beta globulin lower than normal. As the serum proteins are the source of tissue protein, such a disturbance, if pronounced, could lead to cellular malnutrition and atrophy. There is no experimental evidence that the degenerative lesions observed in diabetic persons are due to protein deficiency, but the fact that protein malnutrition may exist in many patients with the disease suggests this possibility.

Disturbances in Fat Metabolism

Disturbances in fat metabolism have been quite common in patients with diabetes. They may involve synthesis of fatty acids or the level of serum lipids. It has long been recognized that fats can be synthesized from nonfat precursors such as carbohydrate or protein and that the liver is one of the chief sites for their synthesis. In untreated diabetes there is a failure to form fat from carbohydrate, and simultaneously fatty acids break down to ketone bodies.[6] The latter breakdown contributes to ketosis, which in turn causes changes in the acid-base balance.

The elevated serum cholesterol in many patients with diabetes is associated with changes in the serum phospholipid content. Many investigators believe the alteration in the cholesterol-phospholipid ratio contributes to the atherosclerosis which is more common among diabetic than among nondiabetic persons.[7] Since 1934, when the fat content of the diet was lowered and the carbohydrate content increased,[8] the incidence of hyperlipemia and of hypercholesteremia has decreased. One rarely sees now the milky serum that was quite common when the high fat, low carbohydrate diet was in use.[9]

Since the use of insulin, many nutritional disturbances in the diabetic patient have been controlled. Xanthoma diabeticorum[10] in which the nodules contain large amounts of cholesterol is almost never seen. But such lesions, which are inherent in the disease, indicate the extent to which the nutritional disorders can proceed.

Disturbances in Vitamin Metabolism

Vitamin A and carotene—A common finding in patients with diabetes mellitus is caro-

tenemia. The peculiar yellowish color of the palms of the hands, on the soles of the feet, and around the alae nasi is evidence of an increase in the serum level of carotene. The average serum level of carotene in diabetic persons has been reported as 0.262 mg. per cent compared with 0.109 mg. per cent for normal subjects.[11] This is not associated with a decrease in the vitamin A levels in the serum. It is interesting that another metabolic disease in which the serum carotene level is elevated is hypothyroidism. It may be that the diabetic patient with carotenemia has some degree of hypothyroidism. In view of the tendency to carotenemia it is well to limit the amount of carrots in the diet. It is also advisable to determine whether or not hypothyroidism is a complicating factor.

Vitamin B complex—Nutritional disturbances affecting fractions of the vitamin B complex are quite common in untreated diabetes and are seen also in diabetic patients whose diets are unusually restricted. Diuresis in uncontrolled diabetes results in a considerable loss of all the water-soluble vitamins as well as calories, minerals and water. The most common deficiencies of the vitamin B fractions seen in diabetic patients are those due to lack of thiamine, riboflavin and nicotinic acid. Experiments have shown that animals deprived of thiamine will exhibit a disorder of carbohydrate metabolism. When a human being is deprived of thiamine, ingestion of glucose is associated with an increase in blood pyruvate and lactate.[12] Lipothiamine, a cofactor containing lipoic acid and thiamine, is essential for the oxidative decarboxylation of pyruvate and also for the oxidation of alpha ketoglutarate to succinate in the citric acid cycle. This explains the accumulation of pyruvic and lactic acids when there is a deficiency of thiamine.

Prior to the use of the liberal diet and to the administration of thiamine to patients with diabetes, peripheral neuritis was common. Although this condition is rarely seen now in the properly treated diabetic, the clinician must appreciate that proper treatment means supplementing the diet with the administration of vitamin B complex.

Riboflavin has many important functions in the body. It is a constituent of a number of enzyme systems associated with metabolism of carbohydrates as well as with other foodstuffs. All the enzymes with which it is concerned function in oxidation-reduction reactions in the body cells.

Riboflavin deficiency with cheilosis and glossitis is still seen in older diabetic persons, particularly those with a history of some disorder in liver metabolism or gallbladder disease. The deficiency may be due to the poor absorption of the vitamin, to loss of the vitamin due to prolonged diuresis, or to increased destruction.

Typical pellagra is not common in diabetic patients at present. When it occurred, it probably was the result of a deficient diet plus the increased excretion of the vitamin due to polyuria. Careful examination of the patient with poorly controlled diabetes often will reveal varying degrees of glossitis or stomatitis. This used to be quite a common finding in the patient with diabetic ketosis. I mention it here because today, due to the more liberal diets and to supplementation with vitamin B complex, the clinician is apt to minimize the importance of these vitamins in maintaining the health and well-being of the diabetic patient. Nicotinic acid, like the other fractions of the vitamin B complex, is important in the carbohydrate cycle and functions as an essential part of the enzyme system concerned with hydrogen transport to the cell. Nicotinamide is the functional group of two coenzymes, namely, codehydrogenase I (DPN) and codehydrogenase II (TPN). Nicotinamide can be synthesized from tryptophan.

There have been several reports on the use of vitamin B_{12} in diabetes.[13,14] Requirements for vitamin B_{12} change with age, and in older persons there apparently is a decrease in absorption and storage of the vitamin. Among its many functions, vitamin B_{12} is concerned with the synthesis of proteins[15] and has a lipotropic effect in rats on a high fat, low protein diet.[3] Leng and Chow[16] reported that hyperglycemia developed in rats receiving diets deficient in this vitamin. Conn and associates[17] observed a decreased glutathione level associ-

ated with an increased blood sugar level when ACTH was given to human beings. In studies on diabetic patients in these laboratories, no relation was found between sulfhydryl levels and blood sugar before and after administration of vitamin B_{12}.[18] Stone and Chow[19] studied the absorption and excretion of radioactive vitamin B_{12} in 40 diabetic patients with and without retinopathy and found that the patients without retinopathy excreted, on the average, a significantly smaller amount of a test dose than did nondiabetic control subjects, whereas the diabetic patients with retinopathy excreted the same amount as the controls. It is concluded that diabetics absorb less vitamin B_{12} from the gastrointestinal tract than normal subjects do, and that diabetics without retinopathy are able to hold onto some vitamin B_{12} while those with retinopathy, lacking a tissue-binding factor, cannot do so; thus the urinary excretion after an oral test dose is essentially normal.

Although experimental data on the role of vitamin B_{12} in diabetes are not conclusive, apparently the vitamin is metabolized differently in this disease. One also has the impression that the requirement for this vitamin is greater than normal.

Disturbances in Electrolyte Metabolism

Disturbances in electrolyte metabolism are seen most often in diabetic patients who have ketosis. Because of the polyuria which accompanies the glycosuria and the ketonuria, loss of sodium increases. Therapy requires the replacement of sodium and fluid. Administration of larger doses of insulin to treat the ketosis is associated with a decrease in the plasma potassium level. This can cause severe muscular weakness, and potassium chloride may be required in the treatment of ketosis. It can be given by stomach tube or in an infusion when indicated.

Discussion

The use of insulin has, to a considerable extent, controlled the nutritional disturbances associated with diabetes mellitus by correcting the major defects in metabolism of carbohydrate, protein and fat. However, the nature of diabetes mellitus is such that the normal metabolic pathways may be interrupted readily, and a breakdown in utilization of the major foodstuffs will occur more readily than it will in persons without diabetes. Further, the large amount of insulin needed to control the glycosuria in severe diabetes creates a situation which may be a factor in disturbing metabolic interrelations. As already mentioned, severe hypoglycemia will cause metabolic changes that alter the nutritional situation in the cells.

The diabetic diet should be designed to supply the substances for which the demand is increased. Supplementing the diet with essential nutrients, such as the various vitamin fractions, is important and will insure an ample supply to maintain intracellular metabolic relations. Adequacy of the nutrition of the diabetic patient is of the utmost importance. Caloric intake should be adjusted to age and occupation and does not differ essentially from that of the nondiabetic person.

In the Diabetic Clinics of the Third (New York University) Medical Division at Bellevue Hospital we have used a liberal carbohydrate diet for young diabetic patients for more than 20 years. For all patients we advise an adequate protein intake, varying from 60 to approximately 85 gm. Fat intake, of course, depends to some extent on the amounts of protein, as meat, even if lean, contains at least 15 gm. of fat per hundred grams. By limiting the amounts of butter and cream, the average fat content varies from 85 to 125 gm.

Diabetics, like other people, find it difficult to adhere rigidly to a diet year after year. For this reason, the diet should be as reasonable as is consistent with good care. The new sulfonylurea drugs have made it possible to use more liberal diets for mild diabetics, and in many cases the disease can be controlled without insulin. Management of diabetes in the future undoubtedly will be influenced by these new hypoglycemic drugs and by a better understanding of intracellular reactions. Application of such knowledge to the requirements of the patient should continue to help control the nutritional disturbances that are inherent in the metabolic disorder associated with the disease.

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NEW YORK UNIVERSITY-BELLEVUE MEDICAL CENTER: View from First Avenue. Low building in front is Alumni Hall, which has a 500 seat auditorium and lecture room. Directly behind is the Medical Science building, housing teaching, research and administrative facilities, and to the right is the 14-story student Residence Hall. At the extreme left is the Institute of Physical Medicine and Rehabilitation. The space between the Institute and the Medical Science building will soon be occupied by University Hospital, which will be the last physical unit of the Medical Center to be constructed.

Pigmented Nevi, Benign Juvenile Melanoma and Circumscribed Precancerous Melanosis

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Chances of malignant transformation of nevus-cell nevi are greater in certain body areas than in others. Danger signals include change in color, size, shape or consistency, diffusion of pigment into adjacent skin, satellite nodules, and lymphadenopathy.

Malignant melanoma resulting in metastases and death is rare prior to puberty. "Benign juvenile melanoma" conveys more clearly the expected course of a clinically benign type of compound nevus.

Outstanding features of circumscribed precancerous melanosis are changeability, irregular outline, and uneven color. A tumor histologically identical to malignant melanoma often develops in such pigmented precancerous plaques.

TODAY, dermatopathologists generally agree with the concept that malignant melanomas arise from melanocytes (melanin-producing cells), usually within so-called junction or compound nevi. It follows that the clinician must make every effort to recognize and to distinguish from the more benign varieties those pigmented nevi *within which malignant melanoma is most likely to originate. More particularly*, he should be alerted to those which are "precancerous," that is, those lesions which in a significant percentile will undergo malignant transformation.

The final answers concerning the origins and pathogenesis of malignant melanomas are still to be found. However, it seems timely to present certain newer and some revived concepts concerning pigmented nevi and related conditions in the attempt to further stimulate thought and interest in this important group of cutaneous neoplasms.

Nevus-cell Nevi

With few exceptions,[1,2] most investigators agree that melanocytes of the skin, eye and mucous membranes are of neuroectodermal origin. Melanocytes which migrate to the skin from the embryonic neural crest may take various histologic forms such as dendritic melanocytes, clear cells, Langerhans cells and nevus cells. Nevi which contain nevus cells are therefore generally pigmented. It is this category of nevus which will occupy our interest in this discussion, since this is the type of structure in which the malignant melanoma usually takes its origin.

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The following types of nevus-cell nevi (lesions bearing nevus cells) are generally recognized: (1) junction nevus, in which the nevus cells are found at the junction of the epidermis and dermis; (2) compound nevus, in which the nevus cells are found in the dermis as well as at the junction of the epidermis and dermis; (3) intradermal nevus, in which the nevus cells are found entirely within the dermis.

In most body areas (exceptions include palms, soles, mucous membranes, genitalia) there is an outspoken tendency for nevus-cell nevi to "mature" spontaneously. Thus, if one follows the natural historical trend of a population of such nevi, it is somewhat as follows:

Most nevi excised from prepuberal children are found to contain junction elements (nevus cells singly or in clusters or "theques" at the dermoepidermal junction). This has been conclusively demonstrated by a number of investigators, including Spitz,[3] Lund and Stobbe,[4] McWhorter and Woolner,[5] and Stegmaier and Montgomery.[6] As nevi grow older, particularly in the postpuberal period, the junction nevus cells migrate downward into the dermis, a process which Unna referred to as *Abtropfung* ("dropping downward"), viz., a downward migration of cells so that in the early phases both junctional *and* intradermal nevus cell elements can be seen. This lesion is then referred to as a compound nevus. The third or intradermal nevus phase is reached when *all* the nevus cell elements are entirely within the cutis and none remain at the dermoepidermal junction. A final late change in intradermal nevi which may take place is the occurrence of progressive fibrosis so that "old" nevi may show a proliferation of fibrous tissue[7] which at times is so profuse that it practically (or actually) pushes the nevus cells out of existence. This latter phenomenon we believe to be the cause of much confusion, in that such intradermal nevi are often misdiagnosed clinically as either "fibromas" or "fibrous nevi."

Further support for this concept of the natural history of nevus-cell nevi is given by the recent work of Stegmaier,[8] who removed and examined histologically all nevi which were found at necropsy in a group of persons over 50 years of age. The number of nevi in this age group was found to be definitely below the average number of nevi in younger adults. This finding supports Stegmaier's thesis that the nevus-cell nevus "is a dynamic lesion, undergoing a cyclic change, capable of an active growth cycle, a period of quiescence and finally complete involution." However, it should be stressed that not all nevus-cell nevi undergo these changes of maturation.

Clinical and histologic examples of some varieties of nevus-cell nevi are depicted in figures 1 to 6.

Much of what has been written in various places about nevus-cell nevi requires clarification or confirmation. Some of the important facts and modern concepts concerning these lesions can be summarized as follows.

1. Nevus-cell nevi are rarely discernible clinically at birth. The vast majority make their clinical appearance in childhood but some do not become evident until adulthood (tardive or delayed nevi, nevi tardi).

2. The vast majority of nevus-cell nevi contain junctional nevus cells in the prepuberal years, whereas most nevus-cell nevi after puberty lack nevus cells at the dermoepidermal zone.[1, 4, 9, 10]

3. When questioned, 20 to 80 per cent of patients who have malignant melanomas recall having had a "mole" at the sites of origin of

the malignant tumors.[11-17] The remainder of such patients cannot recollect such pre-existing "moles" or state categorically that no noticeable lesion preceded the onset of the malignant melanoma. When malignant melanoma arises within a nevus, the patient most often describes the nevus as having been a macular or slightly raised, mottled, brown to slate-gray to jet-black, soft lesion which either was present since childhood or made its appearance later in life.

4. Nevi of the palms, soles, genitalia and mucous membranes tend to retain junction (nevus cell) elements into the later years of life, whereas those on other body areas for the most part undergo "maturation."

5. The average adult has at least 15 pigmented nevi[18] and probably more.

6. Van Scott and associates[19] reported that one-fourth of all the adults they examined had pigmented nevi of the palms or soles, or both.

7. Nevus-cell nevi present a wide variety of clinical features. Their color may vary from normal skin color to pink, tan, brown, blue or black. Their pigment may be evenly distributed or mottled. Their surface may be of different contours, e.g., smooth, uneven, polypoid, verrucose, digitate. Their borders may be even or irregular, well or poorly defined, level with the surroundings or elevated, or may present combinations such as a raised center with a surrounding macular pigmented zone. They can be flat or raised, hairy or hairless, small (less than 1 mm.) or large (half or more of the body, e.g., bathing trunk nevi).

8. When one considers the vast number of nevus-cell nevi which exist, malignant melanoma arising within such lesions is most rare. However, the chances of a nevus becoming malignant are increased in certain sites (lower extremities, nail bed, genitalia, anorectal mucosa[18]); but this alone does not necessarily permit the conclusion that *all* nevi even in such sites should be excised prophylactically any more than it should be recommended that all breasts should be amputated prophylactically in all women over 40!

9. Danger signals to watch for in nevus-cell nevi include change in color (increase or decrease or change in distribution of pigment, or development of erythema), change in size (sudden enlargement in diameter or height), change in consistency (softer, harder), change in surface characteristics (scaling, oozing, bleeding, crusting, erosion, ulceration, infection), occurrence of subjective symptoms (pain, numbness, tingling, burning and, especially, itching), diffusion of pigment into normal skin from the edges of the nevus, development of satellite nodules, and appearance of regional lymphadenopathy.

10. It is quite conceivable that repeated trauma may play a role in malignant transformation within a benign nevus-cell nevus. However, this purely theoretical, widely publicized concept has never been conclusively proved, nor is there any recorded instance of a nevus-cell nevus histologically proved to be entirely benign being traumatized and thereupon becoming malignant.[20]

Therapy of Nevus-cell Nevi

Two of us (V. H. W., A. W. K.[21]) recently described in detail measures for the recognition and management of nevi containing nevus cells. The high lights of these measures may be summarized as follows.

Despite recent advances in the recognition of certain clinical features which are seen in junction nevi, compound nevi and intradermal nevi,[22] in any given instance it is not possible on clinical grounds alone to say with complete certainty that a particular lesion contains or does not contain junction nevus cells. However, the percentage of correct clinical diagnoses increases with the experience and acuity of the clinician. Therefore, in the vast majority of instances the likelihood of serious error in the clinical differentiation among benign, precancerous and malignant tumors bearing nevus cells is reduced considerably when the diagnosis is made by a physician experienced in this field. This is basic to the economical and humane management of these lesions, since the physician who is trained and experienced in diagnosing the nevus-cell nevi and related conditions can justifiably rely on his clinical judgment to decide to which group the presenting lesion belongs and thus avoid unnecessary or unnecessarily extensive sur-

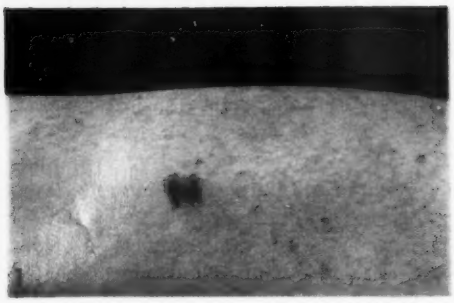
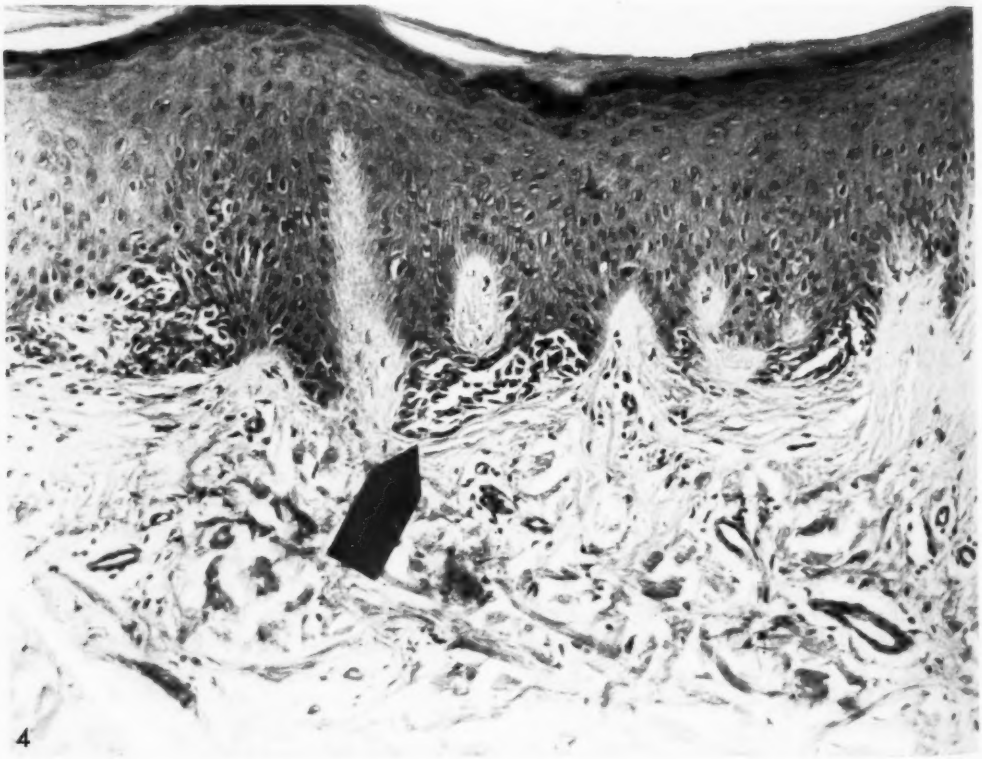


FIGURE 1. Junction nevus.

FIGURE 2. Compound nevus.

FIGURE 3. Intradermal nevus.

FIGURE 4. Junction nevus. Nests of nevus cells (arrow) are seen at the junction of the epidermis and dermis (x 185).



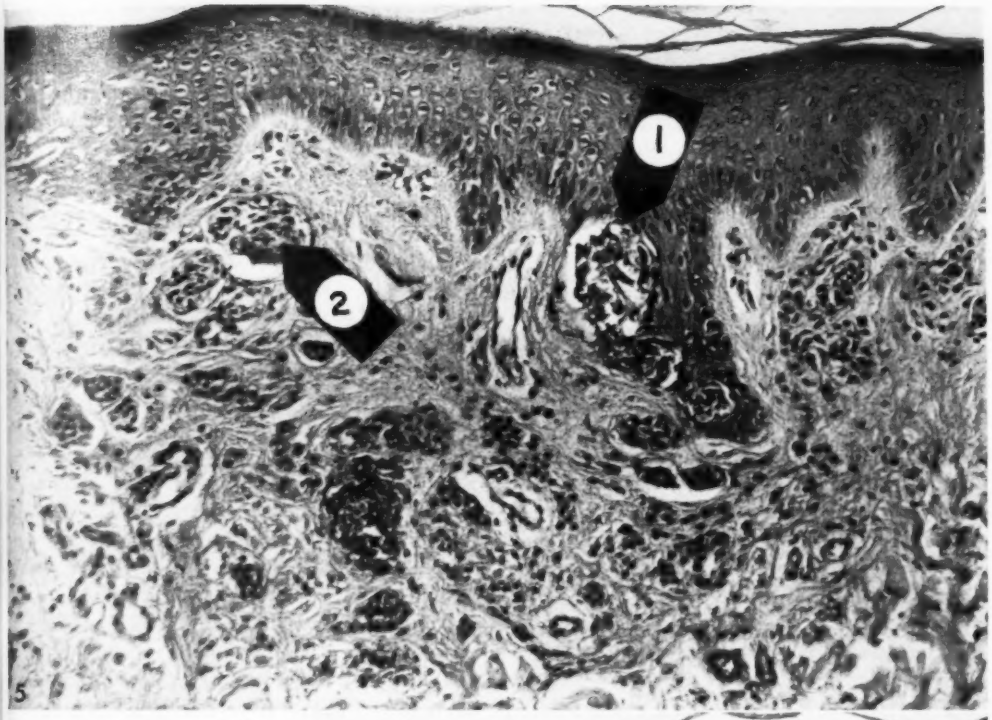


FIGURE 5. Compound nevus. In addition to the junctional nests (1) of nevus cells, isolated nevus cells and clusters (2) of nevus cells have "dropped" into the dermis (x 185).

FIGURE 6. Intradermal nevus. The dermis surrounding the hair follicle and sebaceous glands is packed with numerous nevus cells of uniform size distributed in strands and groups. This type of lesion rarely, if ever, gives rise to malignant melanoma (x 87).

TABLE 1

INDICATIONS FOR THE TREATMENT OF NEVUS-CELL NEVI AND RELATED CONDITIONS

Treatment mandatory:

1. Nevus-cell nevi which have undergone changes or show "activity" such as sudden enlargement, bleeding, inflammation, alteration in color (either darker or lighter), ulceration, crusting, development of satellite pigmented areas, or development of symptoms (especially pruritus or pain)
2. Those showing the above changes during pregnancy
3. Those which histologically show evidence of "unrest," e.g., precancerous junction nevi

Treatment generally considered advisable:

1. Those closely related conditions which are believed to undergo malignant transformation in a high percentage of instances, e.g., circumscribed precancerous melanosis
2. Benign juvenile melanomas

Treatment controversial:

1. Nevus-cell nevi at sites of repeated trauma
2. Nevus-cell nevi appearing after the second decade of life
3. Nevus-cell nevi located on palms and, particularly, soles
4. Nevus-cell nevi at sites where the incidence of malignant melanoma is relatively high, e.g., genitalia, mucous membranes and subungual areas

gery. The clinical appraisal of each nevus demands critical analysis of the differential diagnostic features, a constant awareness of the malignant potentialities, a knowledge of the natural history of such lesions, high regard for past history, utmost care in examination, and, if necessary, re-examination of the lesion.

We by no means wish to imply that even the most experienced dermatologist can rely on his clinical appraisal to distinguish infallibly between all malignant and all benign nevi. But he can rely on his clinical ability to differentiate between indubitably benign lesions and doubtful lesions and, above all, to recognize those features which may indicate possible, probable or frank malignancy. And this ability is, in the last analysis, the all-important one, for it permits the segregation of the benign lesions from the malignant and potentially malignant ones, which then must be examined further by nonclinical procedures and treated appropriately.

Current concepts concerning the indications for treatment of such lesions are outlined in table 1. If a decision is made to treat any of the types of lesions which fall into the groups presented in table 1, surgical excision is the method of choice for their removal when this is feasible. The surgical specimen should then be studied by a dermatopathologist or general pathologist especially interested and experienced in the histologic differentiation of these cutaneous conditions.

When therapy is decided on for those nevi which show the clinical signs of being primarily junctional, it is our practice to excise them conservatively. For the most part these lesions are macular or slightly raised superficial nevi which tend to be medium to dark brown to black in color. Their pigment may be either evenly or irregularly distributed. Surgical excision is also advised for those lesions which are verrucose or centrally raised and surrounded by a peripheral pigmented zone.

In adults by far the largest number of nevus-cell nevi are those which are of purely cosmetic concern. Clinically these are skin-colored to brown, raised (dome-shaped, sessile, polypoid or pedunculated), quiescent lesions of long standing. These lesions can also be surgically excised, but often it is possible to obtain the best cosmetic result by slicing off with a scalpel or scissors that portion of the lesion which protrudes above the skin surface. This procedure also provides a specimen for microscopic examination. If the remaining portion of the nevus is still elevated above the skin surface, light electrodesiccation can be employed to flatten the protruding tissue. In our experience this method is eminently safe and well suited for the management of the benign, primarily intradermal nevi. However, each lesion must be carefully evaluated, minutely examined, and its history ascertained before any such procedure is permissible. There is no substitute for experience in this respect.

Benign Juvenile Melanoma

A diagnosis of malignant melanoma is often a death warrant for the patient. However, dermatologists and others have long recognized that malignant melanoma resulting in metastases and death rarely occurs *prior to puberty*.[14, 15, 23-25a] Moreover, not infrequently

there has been a grave discrepancy between this clinical appraisal by experienced physicians and the pathologist's histologic diagnosis of "malignant melanoma." Out of this chaos, Spitz[3] and Allen and Spitz[26] developed a concept which integrated certain histologic features with the clinical course of such lesions. In 1948 Spitz reported a clinicopathologic study of prepuberal lesions in this group and proposed the term "juvenile melanoma" for a clinically *benign* type of *compound nevus* with certain histologic features which so closely resembled those of postpuberal malignant melanomas that these lesions could easily be confused by the less-experienced pathologist.

Some historical, clinical and histologic characteristics of "juvenile melanoma"* can be summarized as follows.

1. Terminology—Pack[24,27] refers to this type of lesion as "*prepubertal melanoma.*" Grupper and Tubiana[28] suggested the title "pseudomelanoma" since the lesions are not completely limited to the "juvenile" age group (see below) nor are they to be confused with *malignant* melanomas. We feel that the term *benign juvenile melanoma* as used in several remarks by Allen and Spitz[26] and further suggested by McWhorter and Woolner[5] would be preferable, since it more clearly conveys the expected clinical course.

2. Clinical appearance—Benign juvenile melanomas are smooth-surfaced (or occasionally verrucose), raised, hairless nodules which enlarge slowly. They vary in color from pink to red or, less commonly, brown to black. They usually are less than 1 cm. in diameter but may be larger. The margins, although well defined, often are irregular. In about half the patients in Spitz's series the lesions had been present "since birth," and almost all showed slow and gradual increase in size. However, Woringer[29] reported that in his cases the lesions were often of recent onset (2 to 12 months), moderately rapid in growth, pink to brown in color, and characteristically very firm to palpation. Delacretaz and Jaeger[30] also noted this rapid growth in their two cases of benign juvenile melanoma. Shaffer[22] noted that "dome-shaped lesions in the prepubertal period with rapid growth and inflammatory features" often proved to be benign juvenile melanomas.

3. Age—Although, as the name benign *juvenile* melanoma denotes, these lesions are most often seen in young persons, they can occur in adulthood. Allen[31] has seen at least 34 "juvenile melanomas" in adults.

4. Localizations—The majority of reported lesions of benign juvenile melanoma have been on the face. However, all skin areas and even the oral mucous membrane[32] have been the sites of these lesions.

5. Histologic features—The histologic criteria which distinguish benign juvenile melanoma are presented in the works of Spitz and Allen.[1,3,26,33] McWhorter and Woolner[5] reported two predominant types of nevus cells histologically, namely, epithelioid-cell and spindle-cell types. Often there were admixtures of both. In their opinion "perhaps the single most important feature of this group of tumors is the large size of the cell. This feature, more than any other, sets these lesions apart from the common pigmented nevus." However, they emphasized that these large cells do not show the nuclear anaplasia of malignant melanoma despite the fact that mitoses could be found in most specimens. As a group these lesions lacked melanin pigment. In contrast to Allen and Spitz,[33] who reported that about one-third of benign juvenile melanomas could not be differentiated histologically from adult malignant melanoma, McWhorter and Woolner[5] felt that in their series of benign juvenile melanomas "the tumors are recognizable as such and we are of the opinion that they can be separated histologically from the malignant melanoma of childhood."

In 34 benign juvenile melanomas of adults mentioned by Allen,[31] the histologic picture was reported to be "indistinguishable from that of children except for the tendency of some of the lesions of adults to show evidence of involution in the form of interspersed fibrosis."

6. Incidence—The incidence of benign juvenile melanoma is unknown. In a series of 100 nevi *excised at random* from children

*Unless otherwise specified, the material is derived from the papers of Spitz,[3] Allen and Spitz,[26] and Allen's[1] text.

FIGURE 7. Benign juvenile melanoma. Case 1.

FIGURE 8. Benign juvenile melanoma. Case 1. This specimen illustrates many of the histologic findings in this condition, including (1) the combination of junctional and intradermal nevus cells, (2) telangiectatic blood vessels, (3) relatively large size of the nevus cells and multinuclear nevus cells, (4) sparsity of melanin, (5) segregation of groups of nevus cells, and (6) edema in the upper cutis (x 88).

aged 1 to 10 years, Stegmaier and Montgomery[6] did not find a single example of this entity as based on their histologic study. On the other hand, in reviewing 172 consecutive *surgical specimens* of nevi and melanomas in children at the Mayo Clinic, McWhorter and Woolner[5] reported 11 instances (about 6 per cent) of benign juvenile melanomas. However, since most nevus-cell nevi removed in prepuberal children have evidenced a peculiar growth pattern or certain other clinical features to justify their excision, the ratio of the incidence of benign juvenile melanomas to the incidence of nevus-cell nevi in the general population cannot be established on the basis of highly selected surgical specimens. One can only conclude from available data that this type of lesion is uncommon even in children. According to Allen and Spitz[26] the incidence of benign juvenile melanoma drops sharply after puberty.

7. Prognosis—It is important to make it clear that on the basis of present information "juvenile melanomas" in the sense of Spitz

and Allen are *benign compound nevi*. However, further clinical observation will be necessary to establish the natural history of benign juvenile melanomas, and the ultimate prognosis of untreated lesions remains unknown. If, in the prepuberal group, the incidence of benign juvenile melanomas in surgical material is as high as 6 per cent of nevus-cell nevi while benign juvenile melanomas are practically nonexistent in adults, one might assume that as benign juvenile melanomas mature they transform into "ordinary" compound or intradermal nevi.

One provocative feature which bears further evaluation is the fact that Allen and Spitz[26] state that in 5.9 per cent of 362 malignant melanomas "there is noted residual evidence of a preexisting juvenile melanoma." If this finding is substantiated and should benign juvenile melanoma prove to be one of the rarer tumors, their precancerous tendency may be even greater than "ordinary" junction or compound nevi!

However, Allen,[31] a most experienced student of the problem, recently summarized his feelings concerning the outcome of benign juvenile melanomas by stating that "contrary to the conclusion of others, the evidence indicates that there is no more likelihood for a juvenile melanoma to undergo cancerous change in adult life than for any other compound nevus."

Only further clinical and statistical studies will help clarify this most vital point regarding the prognosis and precancerous potential of benign juvenile melanomas.

8. Differential diagnosis—The following are among the conditions which can closely simulate benign juvenile melanoma: other types of nevus-cell nevi, juvenile xanthogranuloma (nevoxantho-endothelioma), fibroma, keloid, lymphocytoma cutis, granulomas (infectious and foreign body), and granuloma pyogenicum.

9. Treatment—We agree with McWhorter, Figi and Woolner[34] that on the basis of the present knowledge of the natural history, precancerous tendency and prognosis of benign juvenile melanoma *conservative* surgical excision is the correct treatment. All experience to date indicates that wide surgical excision or lymph node dissection is not indicated for this condition. Of course the specimen should be examined by a dermatopathologist or general pathologist experienced with the histologic aspects of benign juvenile melanomas and the cutaneous lesions to be considered in differential diagnosis.

Report of case—Case 1—A three year old white girl was first seen at the Skin and Cancer Unit of University Hospital in February 1949, at which time a lesion of six months' duration was noted on the outer aspect of her left leg. The lesion was a soft, sharply demarcated, erythematous, raised nodule about 1 cm. in diameter (figure 7). The clinical diagnosis rendered by the attending dermatologist was "angiofibroma" or "angiosarcoma." In February 1949 the nodule was excised and subjected to histologic examination. The dermatopathologist reported his findings as follows: "In the middle of this section and extending throughout the cutis is a large cellular mass organized somewhat in lobes and somewhat in individual cells. For the most part the cells are large, with large, round, deep-staining nuclei. Multinuclear cells are present. Nests of similar cells can be seen within the epidermis, and in places these cells can be seen coming off the epidermis. There is a large amount of edema in the subepidermic zone. Some pigment is present. Microscopic diagnosis: early nevocarcinoma." Because the tumor cells came close to the line of excision, a further wide excision was performed at another hospital in April 1949. The final diagnosis on review of all the histologic material was benign juvenile melanoma (figure 8). When the patient was last seen in March 1958 there was no evidence of recurrence.

Melanotic Freckle (Hutchinson); Circumscribed Precancerous Melanosis (Dubreuilh)

In 1892 Sir Jonathan Hutchinson[35] described a slowly enlarging ("infective") pigmented plaque ("freckle") on the lower eyelid. The lesion spread over the palpebral and ocular conjunctiva in a woman of about 60 years who had been under his observation for

about two years. In 1894 he[36] reported that a tumor had developed within this pigmented area which after excision was examined microscopically by his son and found to be malignant melanoma. In a series of 32 cases compiled in 1912 by Dubreuilh[37] and designated appropriately "mélanose circonscrite précancéreuse" (circumscribed precancerous melanosis), the lesions appeared to correspond to the one described earlier by Hutchinson. This same entity recently was brought to the fore in the American literature by Klauder and Beerman[38] in their thorough study of five cases and review of the literature. Costello, Fisher and De Feo[39] of our department will soon publish their experience with a group of such patients under the title "Melanotic freckle (lentigo maligna)." The importance of recognizing such lesions prompts us to report in some detail about this condition.

Principal clinical features—The course of circumscribed precancerous melanosis may be divided into two phases, the precancerous or macular stage and the tumor or nodular stage.

Precancerous stage—The precancerous stage begins most commonly in the middle or late decades of life. The lesion usually is situated on the face as a single (or, rarely, multiple) tan or brown macule which, as a rule, slowly enlarges in a rather characteristic manner. It does not appear to arise in pre-existing nevus-cell nevi recognizable or remembered by patients. The three most outstanding clinical features of the precancerous plaque are its *changeability*, its *irregular outline*, and its *unevenness of color*.

The changeability of the precancerous plaque is reflected in the fact that the progress of this pigmented spot is completely unpredictable. The macule may spread slowly, may expand rapidly into surrounding, apparently normal skin, or may even completely disappear spontaneously. However, the most common course is for the pigmentation progressively to cover a larger area, even up to palm size or more, by either slow or rapid spurts of extension.

The second feature, the irregular outline, is based on the lesion's tendency to spread by several different ways, which results in an uneven, jagged configuration. The most common type of pigment spread is by centrifugal "pseudopodal" extension from one point of the periphery of the primary pigmented plaque. Another manner in which the lesion may progress is by the formation and subsequent coalescence of satellite macules. As mentioned previously, some portions of the pigmentation may fade, and this fading may in turn contribute to the bizarre outline. It is, of course, understandable that during certain periods in such a changeable lesion the outline may assume round, oval or other shapes, but it is the *unevenness of the contour* of the lesion which remains a helpful clinical diagnostic clue. Although the perimeter of the lesion usually can be easily recognized because of a sharp contrast between normal skin and the well-defined pigmented border of the melanotic area, at times the transition between the edge of the plaque and the surrounding normal skin is gradual and poorly delineated.

The third important clinical feature, the unevenness of pigmentation, is already apparent at the earliest stages of the formation of the lesion. Generally the pigmented areas will have a fairly uniform *background color* of tan, sepia, light brown or dirty gray-brown on which are superimposed scattered, variously shaped areas (dots, streaks, irregular plaques, entangled lines) of dark brown, blue or black pigmentation. Areas of regression may show lightening of the background hue, loss of the intensity of the color of the superimposed areas of hyperpigmentation, or a complete reversion to normal skin color, sometimes leaving a slight atrophy in their wake.[40]

Other clinical features which may be present are slight scaliness of the surface and mild inflammation surrounding the melanotic plaques. This latter feature may herald the onset of the second (tumor) stage of the disease. Many authors stress the *complete lack of induration* in the precancerous phase.

It is, then, this combination of an acquired, constantly changing, multicolored, large macular freckle with an irregular outline that should make one suspect the diagnosis of circumscribed precancerous melanosis.

Tumor stage—At some point or at several

points within the pigmented plaque, induration and finally obvious tumor formation may develop which histologically has all the features of malignant melanoma. This can occur after a widely varying lapse of time (in Dubreuilh's series from 1 to 34 years with an average of 10 years). The tumor usually is black or dark brown, although on occasions an amelanotic malignant melanoma may be found. A most significant feature of the tumor stage is the fact that as far as metastasis is concerned the clinical behavior does not seem to parallel that of those malignant melanomas which have arisen independently of the lesions of circumscribed precancerous melanosis. Therefore, while the five year survival of all patients with malignant melanomas of the head and neck is reported by Pack and associates[41] as 18 per cent (128 determinate cases), *the prognosis of a malignant melanoma arising within a circumscribed precancerous melanosis of the face has been reported to be excellent.*[17, 37, 38, 42, 43] According to Klauder and Beerman[38] a more guarded prognosis must be made when the malignant melanoma arises within a circumscribed precancerous melanosis that is situated at some site other than the face.

Report of case—Case 2—A 69 year old white woman was first seen in the Oncology Section of the Skin and Cancer Unit of University Hospital in October 1957 because of a "freckle" of the left cheek. According to her history she had noted a pigmented plaque on the left cheek for approximately 20 years. She was quite certain no pigmented nevus or freckle had existed at the site prior to that time. It was her impression that the area of hyperpigmentation originally had been larger and that it had decreased somewhat in size some years prior to her clinic visit. Over the years, the hues of discoloration varied, and some portions were lighter than originally while other portions were darker. About 10 years prior to her visit a nodule appeared which began to bleed periodically and crust over for several months. On examination the patient presented an irregular, well-defined, brownish plaque with hues of tan, brown and black in different areas. The major portion of the lesion was superficial and nonindurated. However, at the upper outer pole there was a 5 mm., raised, smooth, brownish-black nodule which appeared to be well supplied with blood vessels (figure 9).

The lesion was excised in December 1957, and the pathologist reported on the surgical specimen as follows: "The sections show a tumor of the upper corium and an extensively ulcerated overlying epidermis. The tumor consists of nests of closely packed undifferentiated cells possessing rather scanty granular cytoplasm and markedly pleomorphic nuclei and many mitotic figures. Many tumor cells contain melanin, and extend to a depth of about 3 mm. into the corium" (figure 10). "There are peripheral melanocytes at the junction of the dermis and the epidermis at the periphery indicating the primary lesion" (figure 11). "Diagnosis: malignant melanoma within a melanotic freckle."

When the patient was last seen in January 1959 there was no evidence of recurrence of the disease and there was no lymphadenopathy.

Other clinical features—The following brief listing of some other features of circumscribed precancerous melanosis is based on a review of the pertinent literature.

1. Incidence—Circumscribed precancerous melanosis is an uncommon tumor[39, 44] and the incidence is significantly lower than that of junction nevi.[38] However, Miescher[45] reported that *one-fourth to one-third of all his cases of malignant melanoma arose within melanotic freckles.*

2. Sex distribution—Distribution between the sexes is approximately equal.

3. Age of onset—All patients reported have been postpuberal, with ages ranging from 18[37] to 76[42] and averaging about 40.

4. Familial history—Except for one patient in Grinspan and Abulafia's[42] series, in whose family there were two deaths from malignant melanoma, there does not appear to be a familial tendency to the development of circumscribed precancerous melanosis or malignant melanoma.

5. Site—About three-fourths of the lesions which have been reported have occurred on the face, but the condition has been observed

in practically all skin areas,[38, 39, 46] even on mucous membranes.[47, 48] Moreover, the series of cases of "precancerous melanosis of the conjunctiva and skin of the eyelids" reported by Reese[49, 50] are probably closely related or identical to this category of tumors.

6. Etiologic factors—Because of the frequency of occurrence of these lesions on exposed areas, environmental factors (actinic rays, wind, and so on) may be implicated. Trauma preceded the development of some of the lesions reported by Dubreuilh[37] and Walther.[51]

7. Course—According to Klauder and Beerman,[38] *about one-third of these lesions evolve into the tumor stage.* The rest of the lesions they observed remained in the precancerous stage (for the period of time they were followed), and a few of them disappeared spontaneously.

8. Essential histologic features—The precancerous stage may show a variety of histologic findings depending on the area biopsied and the nature of the lesion. The changes in the epidermis may range from simple hyperpigmentation of the basal layer, with an increase in the number of melanocytes or clear cells (*cellules claires*, Masson), to collections of polymorphic melanocytes in localized regions of the basal layer, thereby closely resembling the nests of cells (theques) seen in junction nevi.[38] Mitotic figures are rarely seen. The next phase appears when the melanocytes migrate (invade) from the epidermis into the upper cutis. Miescher[45] believes that such migration indicates beginning malignancy. In the final (tumor) phase the picture is that of malignant melanoma. An inflammatory infiltrate of varying degree, composed mostly of lymphocytes and plasma cells, usually accompanies all the stages mentioned.

9. Differential diagnosis—Other macular or slightly papular tan, brown, blue or black lesions should be considered, including pigmented nevus-cell nevi (those containing nevus cells); pigmented senile keratoses[52]; superficial seborrheic keratoses; café au lait spots as seen in Recklinghausen's neurofibromatosis, Albright's disease and other conditions; Ota's nevus, a variety of blue nevus or Mongolian spot usually involving the face and sclera of the eye which very rarely has been known to undergo transformation to malignant melanoma[53]; senile lentigo; metastatic malignant melanoma; superficial malignant melanoma not arising within a melanotic freckle; and, rarely, ephelis, pigmented basal cell epithelioma, and pigmented Bowen's disease. Senile lentigines are most frequent, occurring in 25 to 30 per cent of persons more than 50 years of age. They are tan to brown macular lesions of exposed areas in the aged and are commonly referred to as "liver spots." Clinically, senile lentigo rarely has the combination and variety of features that are seen in precancerous melanosis and is not prone to transformation to malignant melanoma.[54] However, in the early stages the clinical and histologic differentiation of precancerous melanosis and senile lentigo may be most difficult or impossible.

FIGURE 9. Circumscribed precancerous melanosis. Case 2. (Published with permission of the *A.M.A. Archives of Dermatology.*)

10. Therapy—Precancerous stage—It is of decisive importance to know and to recognize the precancerous stage because it can be, as Miescher[45] says, "completely cured." Until further information is at hand, it appears to us that those lesions whose size and site lend themselves to nondisfiguring conservative surgical excision should be so treated. On the other hand, based on all previous experience, there appears to be justification for destroying the larger lesions by thorough electrodesiccation and curettage,[38] x-ray,[17, 40, 43, 51] radon[43] or radium.[44] It has been our experience and that of others that the lesion may recur at the

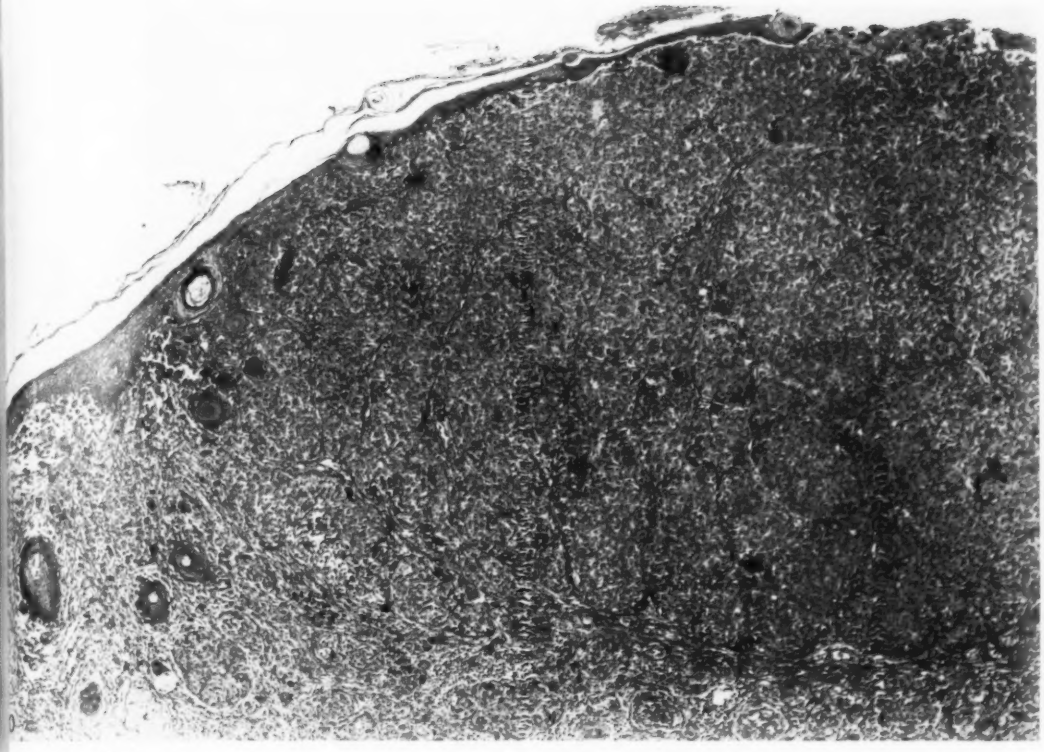


FIGURE 10. Circumscribed precancerous melanosis. Case 2. Photomicrograph of section including nodule shows malignant melanoma invading epidermis and cutis. The cell morphology is markedly irregular and atypical, with numerous mitoses and bizarre nuclear chromatin pattern which bespeak malignant anaplasia (x 75).

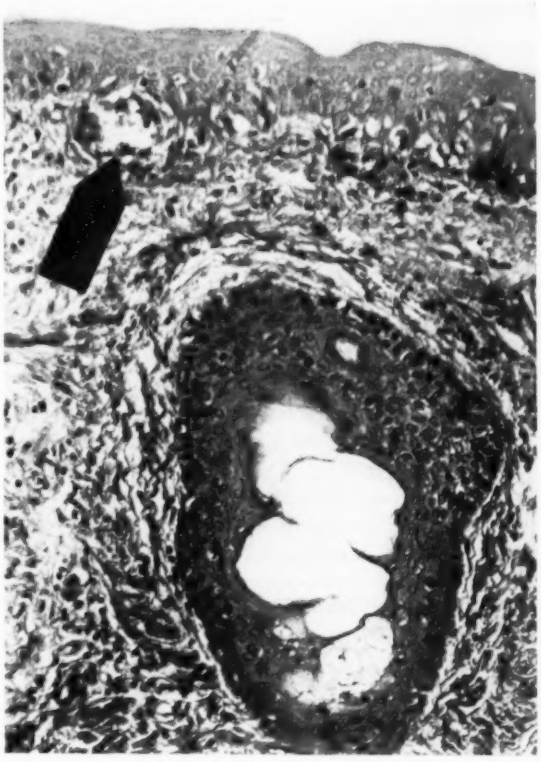


FIGURE 11. Circumscribed precancerous melanosis. Case 2. Section taken from peripheral macular hyperpigmented area showing in the dermoepidermal zone increased numbers of clear cells and melanocytes, some grouped in nests (arrow). There is a mild inflammatory infiltrate (predominantly lymphocytic) associated with a few melanophages (chromatophores) surrounding the pilosebaceous apparatus in the cutis (x 213).

periphery of treated areas despite the complete destruction of the pigmented plaque. This finding does not imply malignant transformation since the histologic features of such recurrent areas remain similar to those seen in the original precancerous phase.

Tumor stage—Because of the relatively good prognosis of malignant melanoma arising within a facial lesion of circumscribed precancerous melanosis, there is a tendency for physicians who are aware of this entity and its properties to do less radical surgical ex-

cisions and to withhold prophylactic lymph node dissection. On the other hand, the data on the comparative end results of therapy of malignant melanomas in precancerous melanosis situated on skin sites other than the face are as yet insufficient to make it certain that conservative measures will regularly suffice to bring about a cure. Therefore, for the present at least, malignant melanomas arising in melanotic freckles in sites other than the face probably should be treated as ordinary malignant melanomas.

Comment

On the basis of a study of the literature and our own experience, we feel that circumscribed precancerous melanosis of Hutchinson-Dubreuilh is a distinct entity to which the American oncologic literature and the nondermatologic literature have not given the attention it merits. In particular, all physicians, pathologists and statisticians should *consider as a specific subgroup those malignant melanomas which arise in circumscribed precancerous melanoses and consider these lesions separately when assessing end results.* From what has been written about these lesions and other types of malignant melanoma, it is our impression that the precancerous phase of this entity is not necessarily synonymous with superficial malignant melanoma,[1,26] malignant lentigo,[11,11a] amelanotic malignant melanoma resembling Paget's disease,[55] or malignant melanoma arising in junction or compound nevi, since these conditions are *already frank malignant melanoma* or malignant melanoma in situ. Dubreuilh himself stated that while in his first publication[56] he used the term "lentigo maligna of old people" (*lentigo malin des viellards*) he later realized that this title was a misnomer because the disease (circumscribed precancerous melanosis) does not always begin in senile persons and in its precancerous phase *it is not malignant.*

Also, without further knowledge of the clinical features, age distribution, anatomic localizations, and so on, we cannot say whether or not some of the so-called precancerous junction nevi[1,26,57] are actually some phase of circumscribed precancerous melanosis.

Surely if, as Miescher has found, one-fourth of all malignant melanomas arise in lesions of circumscribed precancerous melanosis, more such cases should be reported, and these melanomas should be considered separately from malignant melanomas arising in other ways and from other lesions. Only in this way will one add to the present meager information and eventually clarify the many uncertainties which cloud the picture at present.

Summary and Inferences

The concepts of the natural history of nevus-cell nevi (tumors bearing nevus cells) are presented and discussed. Certain clinical aspects, histologic features and approaches to therapy are described.

The current status of benign juvenile melanoma and circumscribed precancerous melanosis is reviewed, and some personal observations and case material are added.

It is hoped that the presentation of these findings and concepts will aid physicians in the recognition and management of these lesions and will stimulate the accumulation of the additional facts needed to establish more firmly the clinical features, course and proper therapy of these conditions.

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Modern Electrocardiography and General Practice

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So far as technical aspects are concerned, physicians need have no immediate concern about any important change in the present method of recording electrocardiograms. New leads under investigation are not yet ready for clinical use, and it may be that in an attempt to get purity of components, systems have been set up which hide clinically important "impurities." The most common error in electrocardiographic interpretation is to make an anatomic diagnosis from the electrocardiogram alone. Perhaps even more serious is the conclusion, reached too often, that a patient whose electrocardiogram is within normal limits does not have heart disease.

THERE are two aspects of electrocardiography about which the conscientious practitioner most often inquires: new methods of collecting and analyzing electrocardiographic data, and new knowledge about the interpretation of the conventional record.

The family doctor reading one of the specialty journals concerned with advances in cardiovascular disease may encounter references to some methods which are unfamiliar to him,[1] such as vector electrocardiography;[2] panoramic, differential, integrative and universal vectorcardiography; and orthogonal lead systems and reference frames such as the cube, the tetrahedron and the trihedron. Naturally such technical terminology arouses his curiosity, and if he can find the time to delve into the original articles he will, in the average case, find many of them beyond his comprehension. Under such circumstances he will become concerned that there may have been some advances in technic of which he should be aware if he is to continue to do a good job in the management of his patients with heart disease. A few remarks, therefore, in a somewhat oversimpli-

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ied manu[illegible], seem appropriate in order to keep the practicing general physician informed of the direction and extent to which fundamental advances are proceeding in the highly specialized area of electrocardiography.

New Technics

Immediately after World War II, several investigators among the physical scientists became interested in the clinical specialty of electrocardiography.[3-6] Compared with the requirements and tolerances of physical systems, the grossness of the more or less empirical method which had flowered under Einthoven and Lewis and had been given its earliest quantitative respectability through the efforts of Wilson and his followers appalled these investigators. Greatest criticism was directed at the leads in clinical use. It was pointed out that such geometrically perfect figures as the frontal triangle, the equilateral or isosceles tetrahedron, or the cube or double cube, though approximately existing in an anatomic sense, were practically nonexistent in an electric sense. The reason is that the source of electric current, the heart, is eccentrically placed in a medium of irregular form and shape, the torso. Under such circumstances, leads in which one electrode is closer to the heart than the other will have a different relative magnitude, for example, compared with a lead in which both electrodes are distant or equidistant from the heart. Until recently, however, no attempt was made to "normalize" these differences, except that many laboratories routinely recorded chest leads, where the electrode is close to the heart, at half-normal sensitivity (1 mv. equals 0.5 cm.) of the recording device to make them comparable in magnitude to the smaller bipolar or unipolar extremity leads recorded at full sensitivity (1 mv. equals 1 cm.).

The physical scientists pointed out another important difficulty. The leads which purportedly took a particular axis—horizontal, vertical or sagittal—of the electromotive force really did not do what was claimed. For example, they were able to show that lead I, the difference in potential between the two arms, was not a true measure of the transverse or x-axis. Interest, of course, in axial components of the heart's electromotive force has sharpened as a result of the ever-increasing need for studying the three-dimensional electrocardiogram. Actually, the study of three dimensions has been done since the advent of the chest leads. Lead I, as already noted, yields roughly the transverse component of the electromotive force, and lead V_F or aV_F the vertical component; the precordial leads give some portion of the sagittal component depending on the region of the precordium from which the lead is taken. Therefore, clinicians have been studying the three-dimensional electrocardiogram for at least a quarter-century.

The engineers and biophysicists, with their admirable and necessary but nevertheless confusing symbolic shorthand, call the axial components x, y and z. Further, they have insisted that the components be obtained in pure form, which means that no axial component is to be contaminated by one or both of the others. This would be particularly desirable where one is trying to record, let us say, an accurate vectorcardiogram in three-dimensional space. If a method were available whereby each rectilinear component could contribute to this vectorcardiogram in pure form and with a magnitude relatively correct with respect to the other two components, a highly quantitative record, in an engineering sense, would be obtained. In designing the leads now available to do this, unfortunately, an assumption had to be made whose validity, in the light of most recent data, is most uncertain, i.e., the one which says the electromotive force coming from the heart may be regarded as originating in a single, fixed-position, variable-moment, finite dipole. This means the heart behaves like a small positive and negative charge as in a voltaic cell, with the differences that the strength can vary and the poles are infinitely close together. Arguments for and against this so-called dipolar hypothesis will not be reviewed here, but one important aspect of the theory should be emphasized: All experiments concerned with the estimation of the inaccuracies of lead systems now in clinical use have been based on experiments in which the source of current was in the first instance re-

garded as a dipole. Herein lies a fallacy which might get the clinician into difficulty if the heart, and particularly the abnormal heart, does not behave as a single dipolar source of current. If a lead system is used which was designed in the first place with a dipole in a model, it is entirely conceivable that this system used on the human body may result in an obscuring of all the nondipolar effects of the heart and actually yield only the electric effects of a single, dominant dipole. This may have some clinical value, but on the other hand it would appear that many of the nondipolar effects or multiple dipolar effects which are suspected to manifest themselves so often in a diseased heart will be entirely hidden by these new quantitative methods of recording electrocardiograms.

The leads yielding the so-called x, y and z components of the heart's electromotive force can be recorded on a linear time scale just like the conventional electrocardiogram, or they can be used to synthesize a vectorcardiogram in space. In either record the nondipolar effects, if present, will not appear.

Herein lies the big question mark in the new era of quantitative electrocardiography. It may be that the physicists and engineers, in their zeal to get purity of components, have actually set up systems which hide clinically important "impurities." In attempting, then, to answer the practitioner's question about new electrocardiographic technics, it can be stated that new leads now under investigation, whether used for making conventional-type scalar records or vectorcardiograms, are not yet ready for clinical use because of the suspicion that they may obscure certain diagnostically useful data.

It may also be asked whether vector records have any advantages over scalar (conventional) records. If the same leads from the body are used for making each, then both records yield the same information but in different form. Which type is used will depend on the interpreting physician's familiarity with the two forms. The scalar record has been familiar to physicians for a longer time, and most experts in the field still prefer it. Vector records do reveal phase differences a little more clearly, and at least in one clinical condition this has been demonstrated to be of value, namely, the differentiation of the electrocardiographic effects of right ventricular hypertrophy and right bundle-branch block by means of the transverse vectorcardiogram. In right bundle-branch block the vectorcardiographic loop usually rotates in a counterclockwise manner and backward; in right ventricular hypertrophy it rotates clockwise and forward. In each situation the lead from the right sternal edge may appear identical. This differentiation is, of course, of considerable interest to the clinician; right ventricular hypertrophy means morbidity but right bundle-branch block undoubtedly occurs in a fairly sizable percentage of the population without heart disease. Actually, these relationships in the vectorcardiogram can be observed in scalar records provided a lead from the right sternal edge is taken simultaneously with a lead from the far left side of the precordium.[1] The availability of instruments for making simultaneous records and the tendency to record at double the conventional film speed of 25 mm. per second reduce the advantages enjoyed by vectorcardiography in revealing this difference.

Advances in *computer technics* almost certainly will be applied to electrocardiography in the future.[7] They will be used not only for collecting electrocardiographic data but also for storing and coding them, and lastly analyzing them. That any of these technics will be available to or even desirable for the practitioner seems quite unlikely. Their use will be limited to large medical centers.

As an over-all conclusion, it would appear that so far as the technical aspects of electrocardiography are concerned the physician need have no immediate concern about any important change in his present method of recording electrocardiograms.

Interpretation

It is not possible in a brief review to give any great detail relative to interpretation. Areas of electrocardiography in which interpretive progress has been made are intraventricular conduction, congenital heart disease, electrolytes and rhythms.[1] Only isolated re-

marks can be made about a few of these.

In regard to intraventricular conduction, it is clear that there can be all degrees of the normal asynchrony of excitation of the two ventricles. Actually the "physiologic right bundle-branch block" seems to become less marked with age, altering somewhat the configuration of the normal electrocardiogram in older age groups.[8] Taking this point of view, it is possible to make analyses and account quite adequately for the deflections in any record depending on the degree of block present or, more correctly, the time difference in excitation of the two ventricles. It is also obvious from such analyses that the dividing lines between normal intraventricular conduction, incomplete bundle-branch block, and complete bundle-branch block are not easy to define, and that the configuration of the QRS complex is more helpful in this regard than the actual duration of the period of intraventricular excitation.

Some interesting concepts of interpretation have evolved in relation to the dynamics of the heart. These relate to the electrocardiographic appearance of so-called overloads on the ventricles. It is maintained that the systolic or diastolic time of the "overload" will determine the electrocardiographic configuration.[9] Further study of the concept is in order.

New data have accrued relative to the effects of electrolytes on the electrocardiogram, and most of the observations relate to the effects of variable concentrations of potassium. Particularly interesting are the unusual S-T displacements sometimes encountered with hyperkalemia on a renal basis. It has been demonstrated that these are reversible if the hyperkalemia can be corrected by use of the artificial kidney. Levine and coauthors[10] called the phenomenon the "dialyzable current of injury."

One of the areas of interpretation in which the practitioner is taking more part and in which there is much difference of opinion is the exercise tolerance test, perhaps better called the electrocardiographic exercise test.[11] It is generally recognized that a man may have a considerable degree of coronary stenosis yet an electrocardiogram recorded while he is at rest may be within normal limits. When such a patient's history is distinctly that of anginal syndrome, an exercise tolerance test will invariably be positive. It is the performance and interpretation of this test which have given rise to a great deal of confusion and diagnostic error.

First, the nature and the amount of exercise requested of these patients by different physicians vary tremendously. The two step test[12] is more or less standard. However, it is not necessary to have two steps. A single step 10 or 12 in. high is all that is needed; a bedside footstool usually serves quite admirably. In performing the exercise the patient steps up and down on this stool 45 times in a minute and a half; in terms of foot-pounds this approximates the amount of work required in the single two step test. From a perusal of referred records it is obvious that physicians' requirements with respect to exercise vary. Some demand only 10 or 15 body bends; others request the patient to hop up and down on one foot 20 or 25 times. Usually, these amounts of effort are inadequate to bring out the electrocardiographic effects of latent coronary disease and cannot be accepted as constituting a part of a valid test. In order to be sure of the results, therefore, the physician must be certain the patient is adequately stressed.

Some physicians probably demand inadequate exercise because of a fear of possible deleterious effects on the patient. Two good guides for preventing these are as follows: (1) The test never should be done until a resting electrocardiogram has been taken and shown to be normal. If it is abnormal at rest, the procedure to be followed depends on the nature of the abnormality. (2) Although a fixed minimal amount of exercise is desirable, if pain should develop during the activity the test should be terminated promptly. Additional precautions would be to have some oxygen and nitroglycerin nearby.

This brings us to a consideration of the technic of recording the postexercise records. Often the practitioner will take the resting electrocardiogram, will have the patient exercise, and then either he or his technician will

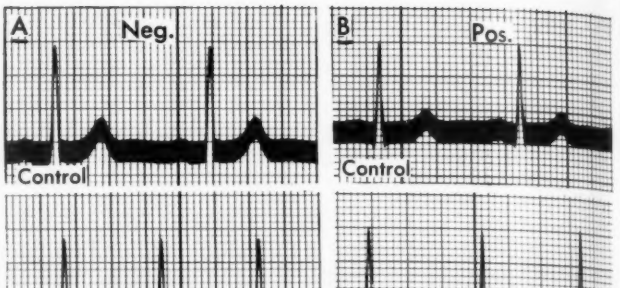

FIGURE 1. Lead V_5 before (above) and after (below) exercise in (A) a 48 year old woman without heart disease and (B) a 70 year old physician with anginal syndrome for 20 years, illustrating negative and positive results, respectively, of an electrocardiographic exercise test. The post-exercise record was made immediately after cessation of the effort in A, and two minutes afterward in B, because in A the lead had already begun to return toward the normal control configuration after two minutes.

To be noted are the S-T junctions and segments in the post-exercise records. Although the S-T junction is lower in B, more important is the planar form and, in this instance, downward slope of the S-T segment, as compared with the upward concavity of this segment in A. The T wave is diphasic in both.

In both electrocardiograms a U wave developed after exercise, but it is upright in A and inverted in B.

again take 12 leads on a single-channel instrument. Obviously to record 12 leads takes a certain minimum of time, and probably several minutes will elapse before the second or third chest lead is reached. In order not to miss important information it is better to record only three or four leads at regular intervals after exercise than to record all 12 leads only once. It is our custom to record bipolar extremity leads I, II and III and precordial lead V_5 immediately after completion of the exercise and again at two minutes, five minutes and nine minutes.

Assuming that the test is performed properly, there is still the problem of interpretation which has given rise to many difficulties even to those quite skilled at such interpretation. It would appear that the criteria for positivity originally set down are inadequate.[11,13] Actually the change in form of the S-T segment (figure 1) is just as important as the amount of its displacement.[14] Further, simple inversion of the T wave as a result of exercise may not necessarily be on the basis of impaired coronary flow. Extrasystoles are of some value, especially if they occur immediately after the exercise but then disappear during recovery. The same remarks apply to the temporary appearance of block, either atrioventricular or intraventricular.

The most common over-all error in interpretation is to make an anatomic cardiac diagnosis from the electrocardiogram alone. A half-century after the introduction of electrocardiography to clinical medicine, it should be generally realized that a correlation between the electric behavior of the heart and the morbidity in that organ is not and indeed never can be perfect.[15] Regrettably this does not seem to be the case, and in their zeal to reach a clinical diagnosis many physicians insist on concluding that a particular record shows right or left ventricular hypertrophy, myocardial infarction, myocardial damage (the most overworked, useless and dangerous of the diagnoses made), or even a congenital abnormality such as tetralogy of Fallot, atrial septal defect or Ebstein's anomaly. An electrocardiogram reveals none of these; all that it displays is the electrophysiologic behavior of the myocardium relative to rate, rhythm, conduction and the basic processes of excitation and recovery. It is too often forgotten that in the early empirical era of electrocardiography a correlation had to be made between the electric behavior of the heart and any anatomic defect that might be present. When a physician states that an electrocardiogram shows evidence of myocardial damage, he is skipping this correlative step and not

taking adequate cognizance of the fact that the electrocardiographic abnormalities on which he is basing his diagnosis may be caused by a great many variables other than anatomic deviation from normal.

Perhaps even more serious than this error is the too frequent conclusion that a patient has no heart disease simply because the electrocardiogram is within normal limits. It would seem unnecessary at this stage of the development of electrocardiographic practice to call attention to such obvious shortcomings of the method. Unfortunately, a continued experience with records interpreted throughout the country makes it plain that the considerable limitations of electrocardiography are still not fully appreciated.

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What Heart Lesions Are Amenable to Surgery?

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Cardiac surgery is undergoing a transition from blind, often palliative procedures to direct-vision operations which are safer, more effective, and in many instances completely curative. These newer operations have been made possible by the use of extracorporeal circulation. Operations inside the open heart may now be carried on, if necessary, for periods of one to two hours. The results, as well as the mortality rate, are much improved.

THE rapid advances in cardiac surgery during the past 20 years and its increasingly important status in the treatment of all kinds of heart lesions make it necessary to review periodically the indications for such surgical therapy. This is particularly important for the general physician, who frequently is the first to recognize these abnormalities.

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Fortunately, along with the improvements in the surgical procedures there have been advances in the methods of clinical and laboratory diagnosis. With few exceptions, cardiac abnormalities of both acquired and congenital origin can be diagnosed correctly preoperatively. The general physician, therefore, not only must recognize as many of these lesions as possible by means of routine procedures, including fluoroscopy and electrocardiography, but also must know when more complicated studies such as angiocardiography and cardiac catheterization are needed. Such complex studies invariably require hospitalization of the patient—more particularly, hospitalization in an institution properly equipped to undertake them. Although the responsibility for selection of patients for cardiac surgery will in most instances be that of someone especially experienced in the field of cardiology, frequently the final decision will rest with the family physician. His knowledge of the patient often will contribute much to this decision, particularly in cases of adult patients, to whom he will be of invaluable aid in deciding for or against surgical treatment.

During the past five years cardiac surgery has been passing through a period of transi-

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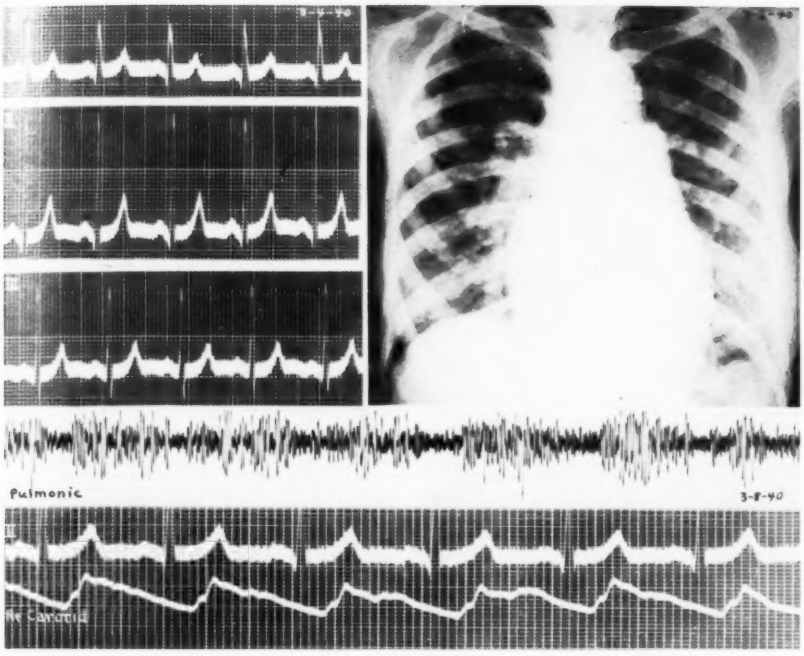

FIGURE 1. Patent ductus arteriosus. R. N., 20 year old woman. Note the essentially normal electrocardiogram and roentgenogram. The stethogram shows a long continuous murmur during systole and diastole.

tion from closed to open technics. Direct-vision cardiac surgery was made possible at first by hypothermia and more recently by so-called cardiopulmonary bypass, a method employing one of the several pump-oxygenators developed for such purposes. In the not too distant future these heart-lung machines quite possibly will completely supplant the use of hypothermia. It is also possible that a few of the closed procedures, such as mitral commissurotomy, will be retained. Direct-vision surgery not only will reduce operative mortality but also will make possible complete, rather than palliative, repair of single and multiple abnormalities. This in turn will influence the general physician's recommendations to his patients with cardiac lesions amenable to surgery.

Patent Ductus Arteriosus

Since it was the successful correction of a congenital malformation, namely, patent ductus arteriosus, some 20 years ago which furnished the initial impetus to the phenomenal strides in cardiac surgery, it seems proper to begin this review with a few remarks concerning this abnormality.

In most instances, patent ductus arteriosus is recognized with a high degree of accuracy by the usual clinical findings. The typical machinery-type, continuous murmur accentuated during systole and fading during diastole, supplemented by electrocardiography and fluoroscopy, suffices for diagnosis (figure 1). Approximately 10 to 15 per cent of these patients, especially infants and children, have other anomalies such as coarctation of the aorta. These other abnormalities may be missed if the patient is not submitted to additional diagnostic procedures such as angiocardiography and cardiac catheterization.

All patients with patent ductus arteriosus, regardless of the presence or absence of symptoms, should be given the benefit of surgical correction. The most desirable age for surgery

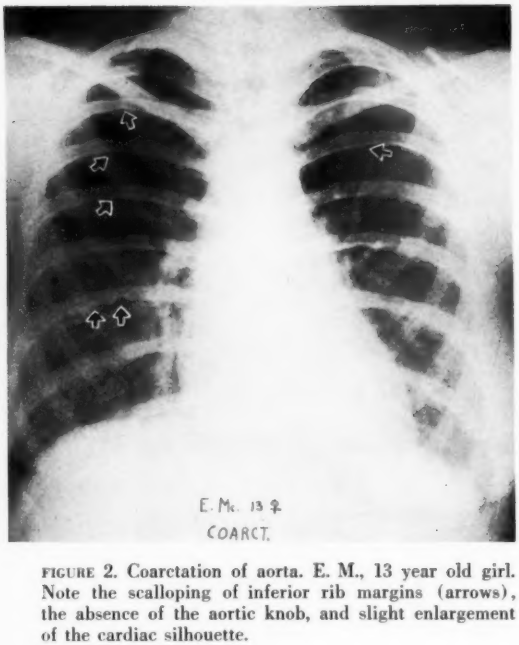

FIGURE 2. Coarctation of aorta. E. M., 13 year old girl. Note the scalloping of inferior rib margins (arrows), the absence of the aortic knob, and slight enlargement of the cardiac silhouette.

is considered to be between 4 and 12 years. A patient of almost any age is eligible for this procedure but the general operative mortality rate of about 3 per cent usually is higher both in adults and in children less than three or four years of age.

Coarctation of the Aorta

Coarctation of the aorta also can be diagnosed correctly in most instances without special studies. Frequently it is the radiologist who makes the initial diagnosis when he finds the characteristic scalloping of the rib margins on a routine chest roentgenogram (figure 2). In other cases a physician first suspects that the lesion is present when he finds an elevated blood pressure in a child or young adult, especially if a loud systolic murmur also is heard. He can confirm the diagnosis quite readily by determining the blood pressure in the lower extremities, which is characteristically much lower than normal in contrast to the hypertension in the arms.

Surgical correction is indicated in practically all cases of coarctation of the aorta. The preferred age is between 8 and 20 years, although some surgeons no longer hesitate to operate on patients past 30 years of age. So-called wear-and-tear sclerosis, so common in patients more than 20 years of age who have coarctation of the aorta, is the deterrent factor in the older patients. Because of the small size of the aorta in infants and in children less than six years old, many surgeons prefer to postpone surgery in such cases unless the hypertension is marked or congestive failure already has occurred. Even including these cases complicated by failure and hypertension, the operative mortality rate is less than 10 per cent, which compares favorably with a rate of about 2 per cent in uncomplicated cases.

As mentioned previously, coarctation of the aorta may be found in patients who also have patent ductus arteriosus. Both lesions can be repaired during the same operation. The anomaly also may be associated with bicuspid aortic valve or aortic regurgitation.

Anomalies of the Aortic Arch

Although many anomalies of the aortic arch are not being diagnosed correctly, it is encouraging to note the increasing number of such patients being given the benefit of surgical correction. They may have a double aortic arch, a persistent right aortic arch, or an anomalous subclavian artery causing, in most instances, compression of the esophagus or trachea. They complain of difficulty in swallowing or breathing or both. Stridor is therefore an important symptom. Fluoroscopically, a barium swallow often confirms the diagnosis. Occasionally the innominate artery or the left common carotid artery may compress the trachea.

All these anomalies can readily be corrected surgically without any limitation as to age.

Atrial Septal Defect

Atrial septal defects, although quite common, are frequently overlooked both in children and in adults. Many of these patients are erroneously thought to have an acquired valvular lesion before the correct diagnosis of an anomaly is made. This indicates that diagnosis of these defects based on physical signs is not

as readily apparent as that of the lesions already discussed. Probably the most striking features are found radiographically. These include prominent hilar shadows with a "dancing" motion and dilatation of the pulmonary artery (which contributes to the broad basal shadow of the heart), and hypertrophy of the right ventricle (figures 3 and 4). The electrocardiogram may show right axis deviation and right bundle-branch block or an arrhythmia such as atrial fibrillation. Special studies with angiocardiography and cardiac catheterization usually are needed to make a final diagnosis and also to rule out such contraindications to surgery as a predominantly right-to-left shunt. Most of the latter patients, however, are cyanotic.

These special studies also may reveal an associated common atrioventricular canal, an interatrial communication with no septum above the mitral and tricuspid valves. Here an open cardiotomy is necessary, rather than the semi-open procedure some cardiac surgeons still consider suitable for repair of uncomplicated atrial septal defects.

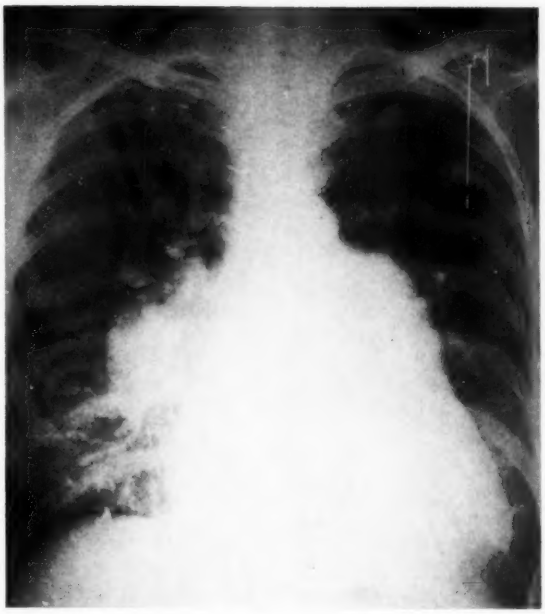

FIGURE 3. Atrial septal defect. A. B., 60 year old woman. Note the marked dilatation of the pulmonary artery, prominent hilar shadows, and enlarged cardiac silhouette, mainly right ventricular in origin.

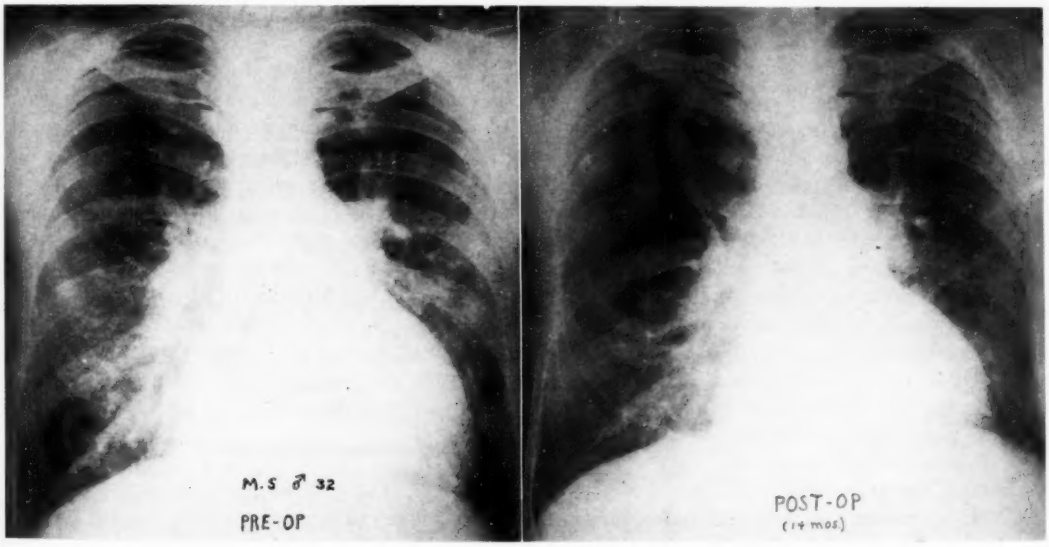

FIGURE 4. Atrial septal defect. M. S., 32 year old man. Preoperative film shows exaggerated pulmonary vascular markings including "dancing" hilar shadows (seen fluoroscopically) and prominent pulmonary artery segment. Film made 14 months postoperatively shows less prominent vascular and hilar markings, a fairly normal pulmonary artery segment, and some decrease in size of cardiac silhouette.

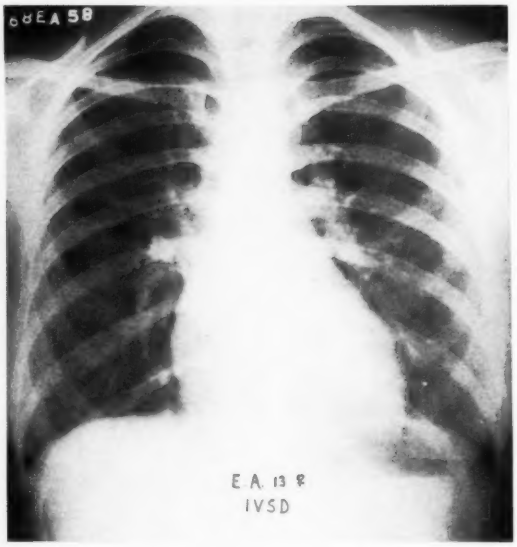

FIGURE 5. Ventricular septal defect. E. A., 13 year old girl. Note enlargement of left ventricle as well as some increase in pulmonary vascular markings.

In view of the low operative risk (about 2 per cent mortality) and because of the difficulty of predicting the future of patients with atrial septal defects, it is probably advisable to recommend surgical correction in all cases.

Ventricular Septal Defect

To date the operative mortality rate for correction of ventricular septal defects has been sufficiently high (about 20 per cent) to warrant considerable thought before advising surgery. However, with open cardiotomy now becoming more widely available, it is likely that a more acceptable over-all operative mortality rate of approximately 10 per cent will be achieved.

For the present, patients with ventricular septal defect who have evidences of definite hemodynamic alterations, and particularly if they also have symptoms, should be considered for surgical correction. This group includes patients with distinct pulmonary hypertension or increased pulmonary blood flow and a large heart (figure 5). In contrast, surgery is *not* indicated for patients with a normal electrocardiogram and a normal chest roentgenogram or a pulmonary artery pressure within normal limits.

Patients with ventricular septal defects quite frequently have associated anomalies, among them atrial septal defect, coarctation of the aorta, patent ductus arteriosus and, of course, stenosis of the pulmonary valve or infundibulum. Most of the patients with the latter anomalies present the malformation known as tetralogy of Fallot.

Tetralogy of Fallot

Pulmonary stenosis frequently is combined with an interventricular septal defect, transposition of the aorta, and hypertrophy of the right ventricle, the combination constituting the tetralogy of Fallot (figure 6). The other combination of lesions sometimes encountered includes pulmonary stenosis, atrial septal defect and an intact ventricular septum.

Tetralogy of Fallot often is readily recognized clinically in children by the clubbing of the fingers, cyanosis and extreme asthenia, and a tendency to squat. Thousands of such children have been benefited by the palliative surgical treatment developed by Blalock and Taussig some 15 years ago. None were returned to normal functional capacity, but nevertheless many were greatly improved by the operative procedure of anastomosing a systemic vessel with an artery to the lung and thereby increasing pulmonary blood flow and, in turn, oxygenation.

In the past few years a small group of children with tetralogy of Fallot have been submitted to open intracardiac surgical treatment, thereby permitting complete repair of the lesions. This undoubtedly will be the treatment of choice in the future, although the over-all operative mortality for the curative procedure probably will be higher than that of the palliative Blalock-Taussig operation.

Pulmonary Stenosis

Pulmonary stenosis not uncommonly occurs as an isolated lesion. It may involve the pulmonary valve, the infundibulum, or both. Most of these patients are not cyanotic. If cyanosis is present, usually there is also an atrial septal defect with a right-to-left shunt. The latter pa-

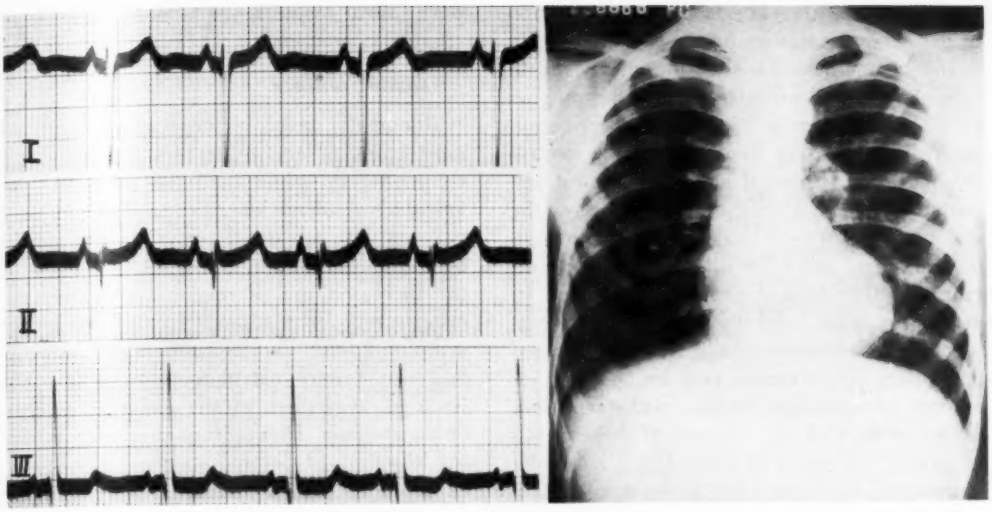

FIGURE 6. Tetralogy of Fallot. P. C., six year old boy. Note the marked right axis deviation of the electrocardiogram, the unusually clear lung fields (pulmonary ischemia) in the roentgenogram, as well as the absent pulmonary arterial segment and rounded apical portion (right ventricle) of the cardiac silhouette (coeur en sabot).

tients should be operated on by direct-vision cardiotomy employing extracorporeal circulation, although a number of surgeons still use hypothermia. Operation is also indicated for those patients with intact septa, but only if the right ventricular systolic pressure is distinctly elevated, as shown by cardiac catheterization.

The usual clinical signs to suggest pulmonary stenosis include a harsh systolic murmur in the pulmonic area, an enlarged right ventricle seen radiographically (figure 7), and right axis deviation on the electrocardiogram.

Mitral Stenosis

Most of the important acquired valvular deformities that are considered amenable to surgical correction are of rheumatic etiology. The most common one is mitral stenosis, which was initially submitted to surgery some 35 years ago but with poor results. About 10 years ago mitral valvulotomy was again introduced, and since then thousands of patients with this lesion have been successfully operated on with good results.

There is little disagreement as to the indications for surgical correction of tight mitral stenosis. By and large, physicians and sur-

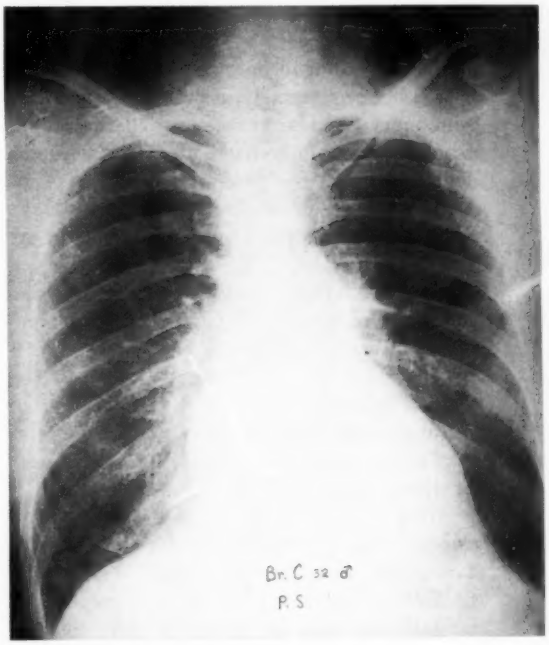

FIGURE 7. Isolated pulmonary stenosis. Br. C., 32 year old man. Note enlargement of cardiac silhouette involving principally the right ventricle and right atrium. There is some diminution of the pulmonary vasculature.

geons agree on the criteria useful in selection of patients with this lesion.

In uncomplicated cases of severe mitral stenosis ("pure" mitral stenosis) the diagnosis is correctly made by clinical examination alone but including fluoroscopy and electrocardiography. Physical signs of greatest importance include a short crescendo presystolic murmur, a sharp or loud first sound, a loud opening snap, and a low-pitched diastolic murmur of rather long duration at the apex. In general, patients exhibiting these classic signs together with symptoms indicative of increased pulmonary hypertension may be operated on without preoperative cardiac catheterization. In the absence of one or more of these physical signs, however, and especially if a systolic murmur is readily audible at the apex, catheterization is advisable to determine the suitability for surgical intervention. Unfortunately, too many patients with borderline clinical findings are being submitted to valvulotomy without benefit of catheterization and with disappointing results.

In the absence of symptoms there is only one valid reason to operate on a patient with mitral stenosis, namely, a markedly increased pulmonary vascular resistance. These patients usually have symptoms related to the hemodynamic alterations produced by such resistance. So-called prophylactic mitral valvulotomy should not be prescribed. However, in the patients with mitral stenosis and systemic embolism, an auricular appendectomy may be done as a prophylactic measure if the stenosis is not severe enough to warrant valvulotomy. Needless to say, patients with obvious signs of mitral insufficiency in the presence of mitral stenosis as based on a loud systolic murmur at the apex with or without a systolic thrill, enlargement of the left ventricle as determined radiographically, and electrocardiographic signs of left ventricular hypertrophy should not be submitted to valvulotomy. In the future, an acceptable surgical procedure undoubtedly will be available for patients presenting evidence of both mitral insufficiency and stenosis and with hemodynamic changes that surgery might be able to correct. Since the advent of open-heart technics, so-called pure mitral insufficiency is now amenable to surgical correction.

Aortic Stenosis

Rheumatic fever is the etiologic basis of most cases of aortic stenosis, but some are congenital in origin, and the latter may be valvular or subvalvular. For the present, only patients with advanced aortic stenosis should be considered for surgery. It is likely that with the increased use of open-heart surgery the criteria will be modified. In the absence of symptoms such as angina pectoris, syncope and heart-failure, valvulotomy probably is not justified, regardless of the apparent severity of the stenosis. This opinion may change with the lessening of the operative mortality to be expected as direct-vision surgery is more widely employed. In any case, operation should not be postponed too long, as operative risk increases once congestive heart-failure occurs.

A loud, rather harsh systolic murmur, most intense at the base, with or without a thrill, usually indicates the presence of advanced aortic stenosis. Systolic blood pressure and pulse pressure usually are low. An aortic diastolic murmur, if soft, may be disregarded. On the other hand, if signs of dominant aortic insufficiency are present as determined by a long, high-pitched diastolic murmur, a wide pulse pressure and considerable enlargement of the heart, valvulotomy is not warranted.

In severe cases of aortic stenosis the electrocardiogram invariably shows alterations, which include inversion of T waves and other signs of left ventricular preponderance or "strain." Arrhythmias are rarely encountered unless there are other valvular deformities such as mitral stenosis.

Only doubtful cases of aortic stenosis need be submitted to special studies, including direct measurement by catheterization of the pressure gradient across the aortic valve. Patients with an associated mitral valvular deformity should be studied rather carefully by special procedures, although with open-heart surgery such combined lesions can be handled quite readily, even if not recognized preoperatively.

Aortic Insufficiency

Until recently, a generally acceptable operative procedure to repair the deformed valve in aortic insufficiency has been lacking. Approximately 350 patients have been treated by the implantation of a plastic ball-valve prosthesis in the descending aorta, as developed by Hufnagel, but the over-all mortality rate has been about 20 per cent. Many of these cases were said to be far advanced, practically in the terminal phase. By and large, this procedure has been too controversial to permit its recommendation without considerable deliberation. With the increasing availability of direct-vision technics it is now possible to correct valvular incompetence at the site of the valve itself. This will undoubtedly make for better results and a concomitant lowering of operative mortality.

It is often difficult to select patients with aortic insufficiency for surgical correction of the valvular deformity. Established criteria have not been available. Probably, patients with marked aortic insufficiency, regardless of its etiology, who present signs and symptoms of progression such as coronary or myocardial insufficiency and who are less than 50 years of age should be considered as candidates for surgical treatment. If at all possible, it is desirable to rule out patients with coronary disease, especially atherosclerosis with progressive stenosis. This is difficult, because aortic insufficiency even in the presence of normal coronary arteries may cause a disturbance in coronary flow and in turn an anginal syndrome or myocardial failure.

ACKNOWLEDGMENT

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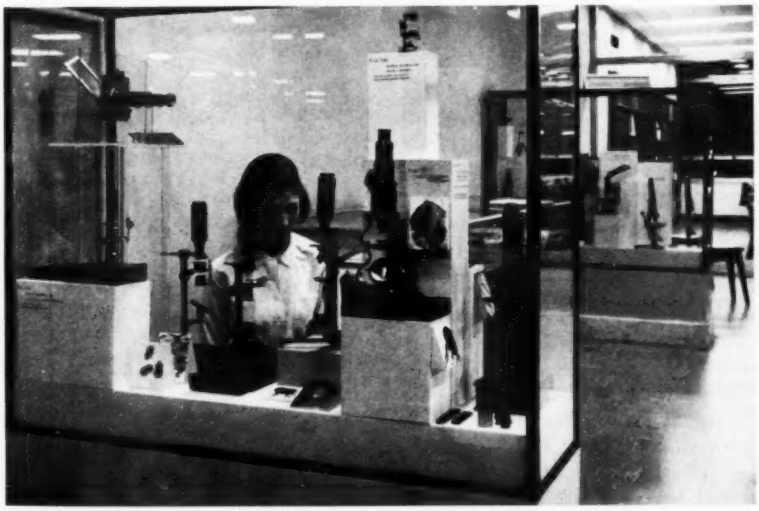

LIBRARY, MEDICAL SCIENCE BUILDING, NEW YORK UNIVERSITY-BELLEVUE MEDICAL CENTER: The Gano Dunn collection of antique microscopes, presented to the Medical Center in 1956 by Mr. Dunn's brother, Harris A. Dunn, honorary trustee.

Some New Chemotherapeutic Agents Reported Useful in Psychiatric Practice

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The newer psychopharmacologic agents facilitate the control of nervous and mental illness but are not a substitute for proper physical, mental or social adjustment of the patient. They are best used as a supplement to other direct measures aimed at obtaining a cure. All of them may produce troublesome, even dangerous side effects or complications.

S. BERNARD WORTIS

THE general practitioner is in a difficult position in regard to the newer psychotherapeutic drugs. Faced with an ever-increasing number of samples of drugs claimed to have remarkable curative properties for a wide range of psychiatric disorders, he is pressed on one hand by some gullible patients to use new "wonder drugs" described in newspapers and magazines, and on the other hand by the commercial drug leaflets, often full of premature and poorly substantiated therapeutic claims. He needs more impartial help and guidance in the use of these newer chemicals which have diverse pharmacologic effects.

To help the physician organize recent knowledge of these psychotherapeutic drugs, the Council on Drugs of the American Medical Association published a revised classification in the March 1, 1958 issue of the *Journal of the American Medical Association* (table 1). However, newer drugs have been added since its publication, and a more comprehensive listing is given herein.

The ideal objective of therapy with psychotherapeutic drugs is to induce an improved mental state with agents which do not produce undesirable subjective effects, toxic side reactions, or harmful summative effects with other drugs.

Many of these new agents are called tranquilizers, ataractics, phrenotropic depressants, psychic energizers, and so on. It is appropri-

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TABLE 1

CLASSIFICATION OF PSYCHOTHERAPEUTIC AGENTS PROPOSED BY AMERICAN MEDICAL ASSOCIATION COUNCIL ON DRUGS, MARCH 1, 1958

I. Antihistamines
  A. Psychotherapeutic antihistamines
    1. Hydroxyzine
II. Central nervous system depressants
  A. Nonselective depressants
    1. Analgesics
    2. General anesthetics
    3. Hypnotics and sedatives
  B. Selective depressants
    1. Anticonvulsants
    2. Antihistamines (as above under IA)
    3. Antitussives
    4. Central muscle relaxants (skeletal muscle relaxants), nonsedative
      a. Mephenesin (AVOSYL®, DIOLOXOL®, Kinavosyl, LISSEPHEN®, MYANESIN®, Mepherol, Mephson, Myoten, MYOXANE®, ORANIXON®, Prolax, Saseral, SINAN®, Spasmolyn, Tolansin, Tolosate, Toloxyn, TOLSEROL®, Tolulox, Toylspaz)
      b. Mephenesin carbamate (TOLSERAM®)
    5. Central muscle relaxants (skeletal muscle relaxants), sedative
      a. Meprobamate (EQUANIL®, MILTOWN®)
      b. Phenaglycodol (ULTRAN®)
      c. Promoxolane (Dimethylene)
    6. Central parasympathetic suppressants
      a. Benactyzine (SUAVITIL®) hydrochloride
    7. Central sympathetic suppressants, phenothiazine derivatives
      a. Chlorpromazine (THORAZINE®) hydrochloride
      b. Mepazine (PACATAL®) hydrochloride
      c. Perphenazine (TRILAFON®) hydrochloride
      d. Prochlorperazine (COMPAZINE®) maleate
      e. Promazine (SPARINE®) hydrochloride
      f. Triflupromazine (Vesprin) hydrochloride
    8. Central sympathetic suppressants, *Rauwolfia* derivatives
      a. Alseroxylon (RAUWILOID®)
      b. Deserpidine (HARMONYL®)
      c. Rauwolfia (RAUDIXIN®, Rauserpa)
      d. Rescinnamine (MODERIL®)
      e. Reserpine (Rauloyidin, Raurine, Reserpine, RESERPOID®, Roxinoid, SANDRIL®, SERPASIL®, Serpiloid)
III. Central nervous system stimulants
  A. Methylphenidate (RITALIN®) hydrochloride
  B. Pipradrol (MERATRAN®) hydrochloride
IV. Miscellaneous agents
  A. Azacyclonol (FRENQUEL®) hydrochloride

ite to state at once that none of these new chemical agents truly fits all these categories, nor can it be said that any one agent precisely helps all forms of psychiatric illness. One of the greatest problems of modern psychiatry is the lack of agreement on a single hypothesis for the pathogenesis of mental illness. Added to this factor is the highly subjective nature of most measurements of clinical improvement. These two factors have done much to complicate present-day study of newer psychopharmacologic agents. However, even the more skeptical clinical psychiatrists now agree that these drugs facilitate the control of nervous and mental illness in a way not possible before their use. Also, there is increasing agreement that these new drugs do not correct the basic psychotic process in a permanent way.

A few simple rules should guide the physician in the use of these drugs:

1. Do not fall into the habit of prescribing a tranquilizer or sedative or stimulant for every slight emotional tension state.

2. These drugs are not a substitute for proper physical, mental or social adjustment of the patient.

3. These drugs are not specifically curative; their best use is as a supplement to other direct measures aimed at obtaining a cure.

4. Since many of the agents in a special group have similar clinical effects, it is better to learn to use one or two in each group skillfully rather than to use many with no feeling of secure knowledge of their effectiveness or complicating side reactions.

For practical considerations and use, one may list these newer drugs under several headings (table 2).

Phenothiazine Derivatives

These important tranquilizers vary greatly in potency from the strong mepazine, prochlorperazine, thiopropazate and perphenazine to the weaker chlorpromazine, promazine, promethazine and trifluprazine. All these have been reported useful in the treatment of the major psychiatric disturbances. Side effects vary with the dosage and variety of the phenothiazine used, but most of the drugs can produce hypotension, tachycardia, dryness of the mouth, sluggishness, and skin rashes (light sensitivity). More rarely (in 1 to 2 per cent of patients) one sees a type of obstructive jaundice which is usually benign and recedes when the drug is stopped. Agranulocytosis is

TABLE 2

A List of Some of the Newer Psychopharmacologic Agents

DRUG GROUP	CHEMICAL NAME	REGISTERED OR PROPRIETARY NAME
	Groups of drugs considered to be major tranquilizers	
Phenothiazine derivatives	Acepromazine	Plegicil (in Canada)
	Chlorpromazine (pronounced antiadrenergic action)	Thorazine, Largactil (in Canada)
	Levomepromazine	Nozinan (in Canada)
	Mepazine	Pacatal
	Perphenazine	Trilafon
	Prochlorperazine	Compazine, Stemetil (in Canada)
	Promazine	Sparine
	Promethazine	PHENERGAN®
	Thiopropazate	DARTAL®
	Trifluperazine	Stelazine
	Triflupromazine	Vesprin
Rauwolfia serpentina alkaloids	Crude drug	Raudixin
	Purified extract	Rauwiloid
	Deserpidine	Harmonyl
	Canescine	
	Recanescine	
	Raunormine	
	Reserpine (releases intracerebral serotonin)	Serpasil, Sandril, Reserpoid, Serpiloid, SERFIN®
	Rescinnamine	Moderil
	Groups of drugs considered useful as minor tranquilizers	
Diphenylmethane derivatives	Azacyclonol	Frenquel
	Benactyzine (marked anticholinergic action)	Suavitil
	Doxylamine	DECAPRYN®
	Hydroxyzine	ATARAX®
	Phenyltoloxamine	P.R.N.
Propanediol and butanediol derivatives	Mephenesin	Tolserol
	Meprobamate	Equanil, Miltown, MEPROSPAN®
	Phenaglycodol	Ultran
Some newer antidepressive (stimulant) drugs	Deanol (said to be a precursor of acetylcholine)	DEANER®
	Imipramine	TOFRANIL® (G22355)
	Iproniazid (inhibitor of monoamine oxidase)	MARSILID®
	Methylphenidate	Ritalin
	Pipradrol	Meratran
Some newer hypnotics and sedatives	Captodramin	Suvren
	Ectylurea	NOSTYN®
	Ethinamate	VALMID®
	Ethchlorvynol	PLACIDYL®
	Glutethimide	DORIDEN®
	Methylparafynol	DORMISON®
	Methylpentynol	Oblivon
	Methyprylon	NOLUDAR®
	Oxanimide (a glycidamide)	Quiactin

a more serious complication, seen about once in every 50,000 patients. Parkinsonism and other extrapyramidal signs and symptoms occur in many patients when larger doses are given for long periods. The more potent the phenothiazine used, the more rapid and more frequent is the development of an extrapyramidal picture, which usually clears promptly

after the drug is stopped. In some patients under phenothiazine medication an unrelated coronary infarct may occur that will remain silent, without symptoms.

All these drugs have a calming effect and increase appetite and may induce constipation. They are effective in patients with excitement, agitation, active disturbing hallucinations, and overactivity. *They are not valuable in treating depressive symptoms.* The more potent phenothiazine derivatives are useful as antiemetic agents in the treatment of central nausea, anorexia and vomiting and have been found effective against persistent hiccups. Many have antipruritic effectiveness in the management of neurodermatitis. Chlorpromazine has also been used with success by some physicians to treat asthmatic attacks and relieve acute and chronic porphyria.

The phenothiazines are readily absorbed from the gastrointestinal tract; they are mainly metabolized by the liver, and small amounts appear unchanged in the urine. Care should be exercised in giving these drugs to patients with liver disease or damage, although moderate renal damage is not a contraindication to their use.

Rauwolfia Alkaloids

Much work has gone into the production of purified preparations of *Rauwolfia serpentina*. There are three crystalline derivatives—reserpine, deserpidine and rescinnamine. These slow the heart, lower blood pressure, increase hydrochloric acid secretion in the stomach, stimulate peristalsis (large doses may cause cramps and diarrhea), increase salivation, induce miosis, affect the temperature-regulating center, and calm the patient. Large doses can produce nasal stuffiness, nightmares, mental slowing and parkinsonism. Serious drops in blood pressure may occur in patients taking these drugs when a general anesthetic is given, and therefore one must be sure to discontinue the drug at least 7 to 10 days before any surgical procedure requiring general anesthesia. The drugs are slow to act but prolonged in their effect.

The *Rauwolfia* alkaloids are useful for the tense, mildly hypertensive, apprehensive, anxious patient. Like the phenothiazines, they stimulate appetite. They are capable of initiating or intensifying mental depression.

Do not use these drugs in depressed patients. Use them sparingly if at all in patients with a history of peptic ulceration or gastrointestinal irritability.

Reserpine releases serotonin from brain, blood platelets and intestinal tract, and some observers postulate that its therapeutic action is mediated by this chemical mechanism.

The metabolism and elimination of the *Rauwolfia* alkaloids are not thoroughly understood.

Diphenylmethane Derivatives

The diphenylmethane derivatives are among the minor or weaker tranquilizers. Azacyclonol has been found useful in controlling some patients with toxic delirious states showing confusion, anxiety and hallucinations. It was noted that this drug could prevent the experimentally induced hallucinations invoked by lysergic acid diethylamide (L.S.D.) and mescaline. It prolongs barbiturate-induced sleep, will correct electroencephalographic abnormalities produced by L.S.D., and will antagonize hyperactivity produced by pipradrol, a central nervous system stimulant.

Benactyzine and hydroxyzine have chemical structures and pharmacologic actions similar to those of the antihistamines. They also potentiate barbiturate action, block conditioned reflex activity, and induce sedation. These agents are effective mainly in mild psychoneurotic conditions to treat mild fear and anxiety states.

Benactyzine may produce atropinelike side effects, and in some persons it has produced an unpleasant feeling of detachment from reality (depersonalization). Benactyzine is said to block a recycling (obsessive rumination) of thought processes. It produces difficulty in concentration and some hesitancy of speech, heaviness of the limbs, and change in time perception. It is a cholinergic blocking drug with effects that are similar to adiphenine (TRASENTINE®).

Hydroxyzine produces drowsiness, reduces spontaneous motor activity, and prolongs barbiturate-induced sleep. Few side effects other

than drowsiness have been reported.

Some investigators have reported encouraging results with phenyltoloxamine in some chronic schizophrenic patients. This drug resembles hydroxyzine in possessing antihistaminic actions with a large central sedative component.

This group of drugs is still under much study, and our clinical and pharmacologic knowledge of them is still limited.

Propanediol and Butanediol Derivatives

Meprobamate resulted from research efforts to prolong the transient effective action of mephenesin by esterification with carbamic acid. It has peculiar pharmacologic properties between mephenesin and the barbiturates. It is a spinal interneuronal depressant and therefore a muscle relaxant, and has a depressant effect on multisynaptic reflexes. Meprobamate is an anticonvulsant, acting to synchronize and induce a slow wave pattern in the electroencephalogram in the diencephalic region. It has been used in the treatment of petit mal epileptic seizures; however, grand mal seizures can result from sudden withdrawal of meprobamate (as with barbiturates) after prolonged high dosage in man. Prolonged use of the drug in some persons can result in other withdrawal symptoms such as psychologic dependence and tolerance. It has no anticholinergic, antihistaminic or adrenolytic action, in contrast to the phenothiazines and *Rauwolfia* alkaloids. It does not enhance barbiturate-induced sleep, nor does it inhibit some conditioned reflexes.

The side effects include drowsiness, hypersensitivity reactions, occasionally acute intoxication and withdrawal effects.

Phenaglycodol resembles meprobamate in depressing multisynaptic reflexes and possessing anticonvulsant properties.

Antidepressive (Stimulant) Drugs

This group of drugs is said to increase activity of various portions of the nervous system. They differ with respect to mechanism and locus of action. Whereas we have many drugs that are central stimulants, the number employable clinically without unpleasant side effects is small. Caffeine, the amphetamines, nikethamide, and pentylenetetrazol are now well known.

Some of the newer drugs, such as deanol (said to be a precursor of acetylcholine), imipramine (whose exact action on the brain is not known), iproniazid (said to increase the serotonin and norepinephrine in the brain and to be a powerful monoamine oxidase inhibitor), methylphenidate and pipradrol (both piperidine derivatives), have many psychopharmacologic properties similar to amphetamine but with fewer peripheral autonomic effects. These last two compounds probably are subcortical rather than cortical stimulants by their action on the reticular activating system.

Excessive dosage with iproniazid may lead to jaundice (possibly liver damage) or an acute psychotic reaction. It should not be used in hyperactive, agitated patients or those with epilepsy or impaired kidney function. Avoid giving the drug together with an anesthetic, cocaine, meperidine or any other amine oxidase inhibitor.

These drugs have been used to combat depressive moods, fatigue and lethargy.

There is great need for a safe, effective antidepressive drug.

Some Newer Hypnotics and Sedatives

More and carefully controlled studies are needed for a better evaluation of this group of drugs. Captodramin recently has been reported as useful in treating brain-damaged restless children with difficult behavior problems. Ectylurea is a mild sedative useful to control mild anxiety, tension, restlessness and irritability. It is less useful in excited patients. This drug is rapidly absorbed and metabolized. Thus far, habituation or cumulative effects have not been reported. Glutethimide, methyprylon and ethchlorvynol are sedative in small doses and hypnotic in larger dosage. They are central nervous system depressants. Anorexia, nausea, mental confusion and ataxia have been seen with their use, and some skin rashes have been reported with glutethimide. Oxanimide behaves like a short-acting barbiturate, with a calming effect in anxiety states.

Some General Principles in Use of Psychopharmacologic Agents

1. First, distinguish between the use of these drugs for major psychiatric therapy and their use for minor psychiatric therapy. The major conditions include psychotic reactions, schizophrenia, manic reactions, panic states, delirium and *severe* psychoneurotic illness. The minor psychiatric conditions include psychoneuroses, with anxiety and phobic states.

2. All psychotherapeutic drugs may produce side effects or complications that may be troublesome or even dangerous. The physician should acquaint himself with these possible reactions for the drug he is prescribing. The *Rauwolfia* alkaloids and the phenothiazines may produce an extrapyramidal syndrome (parkinsonian syndrome), jaundice, agranulocytosis and skin reactions. Some persons may become habituated to the meprobamate preparations.

3. All tranquilizing drugs aim to relieve anxiety, tension, agitation, restlessness and overstrong, emotionally aggressive activity. In the management of neurotic anxiety the drugs are useful largely as an aid to psychotherapy. For the major psychiatric conditions, major tranquilizers are used to induce symptomatic sedation.

4. Clinical experience is accumulating in regard to the use of antidepressants (stimulants). Before undertaking treatment with one of these drugs, make certain the patient is not a serious suicidal risk requiring immediate psychiatric hospitalization. If the depressive state is not serious enough to require hospitalization, drug therapy or electroconvulsive therapy combined with psychotherapy may be undertaken.

5. The newer sedatives and hypnotics are worth consideration in conjunction with, or in place of, some of the older sedatives which have been well tested.

General Recommendations

For the general practitioner's information, the following listing is suggested. It would be wise to consult a psychiatrist for more specific recommendations.

Schizophrenic, manic and acute toxic hallucinatory reactions—Drugs reported useful in these conditions are (1) the phenothiazines, (2) the *Rauwolfia* alkaloids, and (3) azacyclonol. Some of these drugs may have disturbing side effects about which the physician should be alerted.

Psychoneurotic reactions—Drugs reported useful in the treatment of psychoneurotic reactions are (1) diphenylmethane derivatives and (2) propanediol and butanediol derivatives. These drugs have a minimum of side effects and produce neuromuscular relaxation and diminution of anxiety with very little drowsiness.

Depressive states—Drugs reported effective in the treatment of depressive states are (1) deanol, (2) imipramine, (3) iproniazid, (4) methylphenidate and (5) pipradrol.

Hypnotic and sedative effects—A list of some newer drugs used for hypnotic and sedative effects is given in table 2.

Stabilization in the Low Back Complex

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Derangement of the small muscle-ligament system of the back can cause local and peripheral pain. Injection of hydrocortisone in the interspinous space which exhibits the most tenderness permits localization of the affected level and gives some idea of the degree of derangement; it can also help distinguish pain of continuing root pressure from the referred pain of a sprung back.

DESPITE advances in conservative management and operative technics the understanding of the low back complex still poses problems. The term "low back complex" includes those derangements which cause local pain with or without peripheral radiation. It excludes derangements of infectious or neoplastic origin. The frank herniated disk with unremitting radiculopathy does not present a problem, since the surgical indication is explicit. A lesser degree of derangement, in particular the sprung back, is the subject of this presentation.

An incomplete knowledge of the natural history of the low back complex, changing concepts in the attribution of pathology, and inability to quantify the pathology make for difficulties in the management of low back problems. These difficulties can be illustrated by the shift in major attention away from the sacro-iliac joint in the last 30 years. In the recent past, pain at the posterior projection of the sacro-iliac joint was attributed to derangement of that joint. The same pain is now more generally ascribed to tenderness of the insertion of the erector spinae group in the vicinity of the sacro-iliac joints secondary to a lumbosacral strain.

Another difficulty in clinical management

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From the Neuro-Muscular Study Group, New York University-Bellevue Medical Center. Supported by the Charles A. Dana Foundation.

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arises from the fact that a fair number of successes and failures in treatment occur regardless of whether the starting premise puts the pathologic process in the sacro-iliac region or in the lower lumbar region. Manipulation and supports may help irrespective of their anatomic designation. This is the confusion of attribution.

As already noted, the bulk of the present thought has localized the common low back derangement to the lower lumbar area. In this current thinking, the sacro-iliac joints are absolved other than for discrete demonstrable pathologic process. In justice, it can be said that better results have been achieved since the evolution of present concepts. Thus, lumbosacral strain has evolved as the common denominator to explain numerous back difficulties. Depending on the physician's orthopedic background, the connotation of this strain is either a ligamentous disturbance in the area or that the region is simply the focal point of disturbed force relationships (gluteal, hamstring, psoas, abdominal and erector muscles). This latter view is responsible for emphasis placed on the pelvic tilt. A brief consideration of the pertinent anatomy will be helpful in understanding the functional pathology of the low back complex.

The deep back musculature, at first glance unreasonably complex, can be simplified into two groups, the short and the long muscles. The short muscles are attached to the vertebral processes of adjacent vertebrae. The long muscles cross a number of vertebral segments. The short muscles and their associated ligaments bind the contiguous vertebrae together. These units set the fulcrum by stabilizing those segments against which the long muscles exert their force, to cause gross motions.

Understanding of the hypothesized role of these anatomic units can be helped by illustration with analogies. In figure 1, fireman B is trying to raise the ladder by walking forward under it. Unless fireman A establishes a fulcrum, B's efforts will result in a purposeless forward motion of the ladder. This analogy of a single fulcrum is somewhat oversimplified. Segmental stabilization must be maintained at every intervertebral joint. If this were not so, the long muscles would pull the spine down into collapsing curves (figure 2). The so-called idiopathic juvenile scoliosis illustrates the result of multicentric stabilization failure.

Figures 3 and 4 are schematic representations of the short muscle-ligament system (4a, spinalis; 4b, multifidus; 4c, transversalis). This binds the joints (figure 3; Z,Z') together, reinforcing the ligament system to set the fulcrum for motion. If the pivot point is poorly stabilized, the long muscles do not function properly. Remember that a great portion of the long-muscle action is usually involuntary. If the fulcrum mechanism is associated with an inflammatory reaction in either the short muscle-ligament system or the joints, the stabilization of the area will be painful. Contraction of the long muscles may end in spasm in a futile attempt to erect the spine against the inadequate fulcrum. The fulcrum systems must be adequate not only for motion of the spine itself but also for maintenance of posture. The long-muscle system acting against the intrinsic fulcrum units is the basis of group stabilization for the action of other muscles (gluteal, hamstring, abdominal). In the absence of trunk stabilization, the associated musculature cannot function properly. This improper or inadequate function is ultimately reflected in varying degrees of muscular decompensation.

Newman[1] has used the term "sprung back" to describe an inadequacy of the supraspinous and interspinous ligaments. Herein, the term has been given a broader scope to include derangement of any portion of the short muscle-ligament system. We believe this license in use of the term is justifiable on clinical grounds.

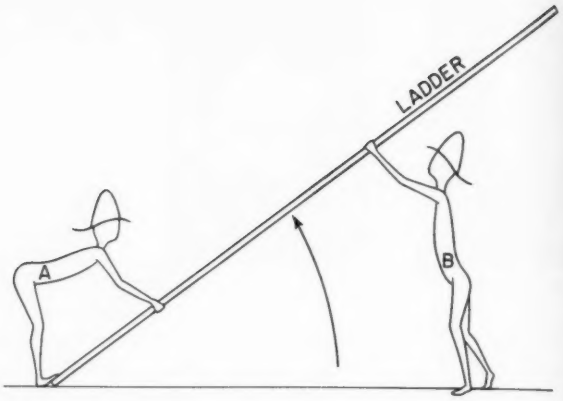


FIGURE 1. Fireman B cannot erect the ladder by walking forward unless fireman A establishes the fulcrum.

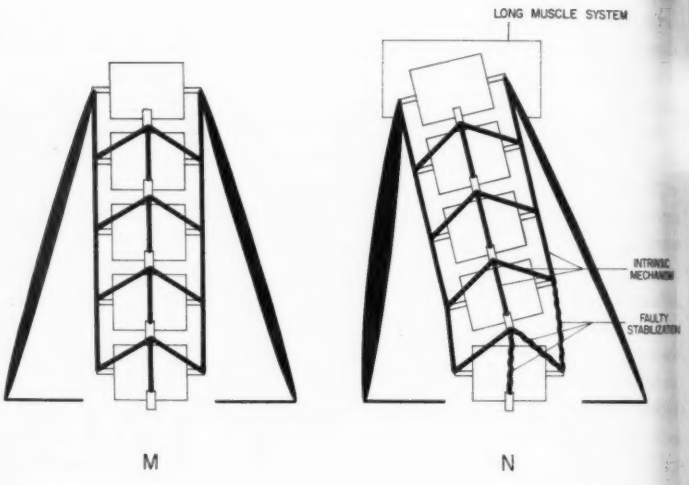


FIGURE 2. M. Action of long muscles with back stabilized. N. In presence of faulty stabilization, action of the long muscles causes a scoliosis.

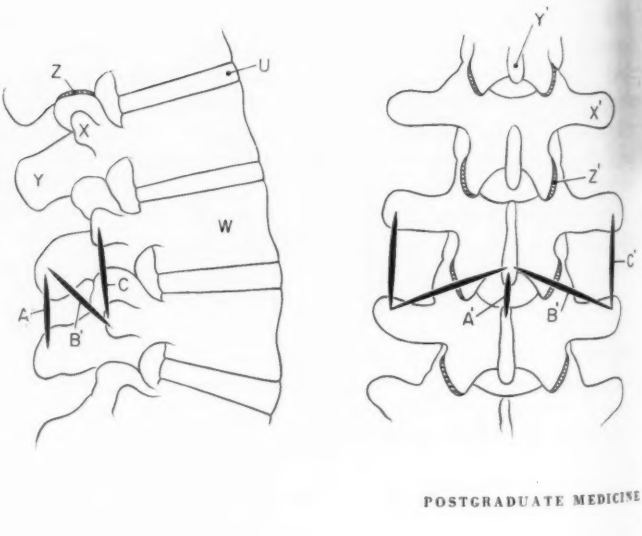


FIGURE 3. Schematic representation of the stabilization mechanism. W, ventral body; U, intervertebral space; Z, Z', facet joints; A, A', spinalis muscle and interspinous ligament; B, B', multifidus muscle; and C, C', transversalis muscle.

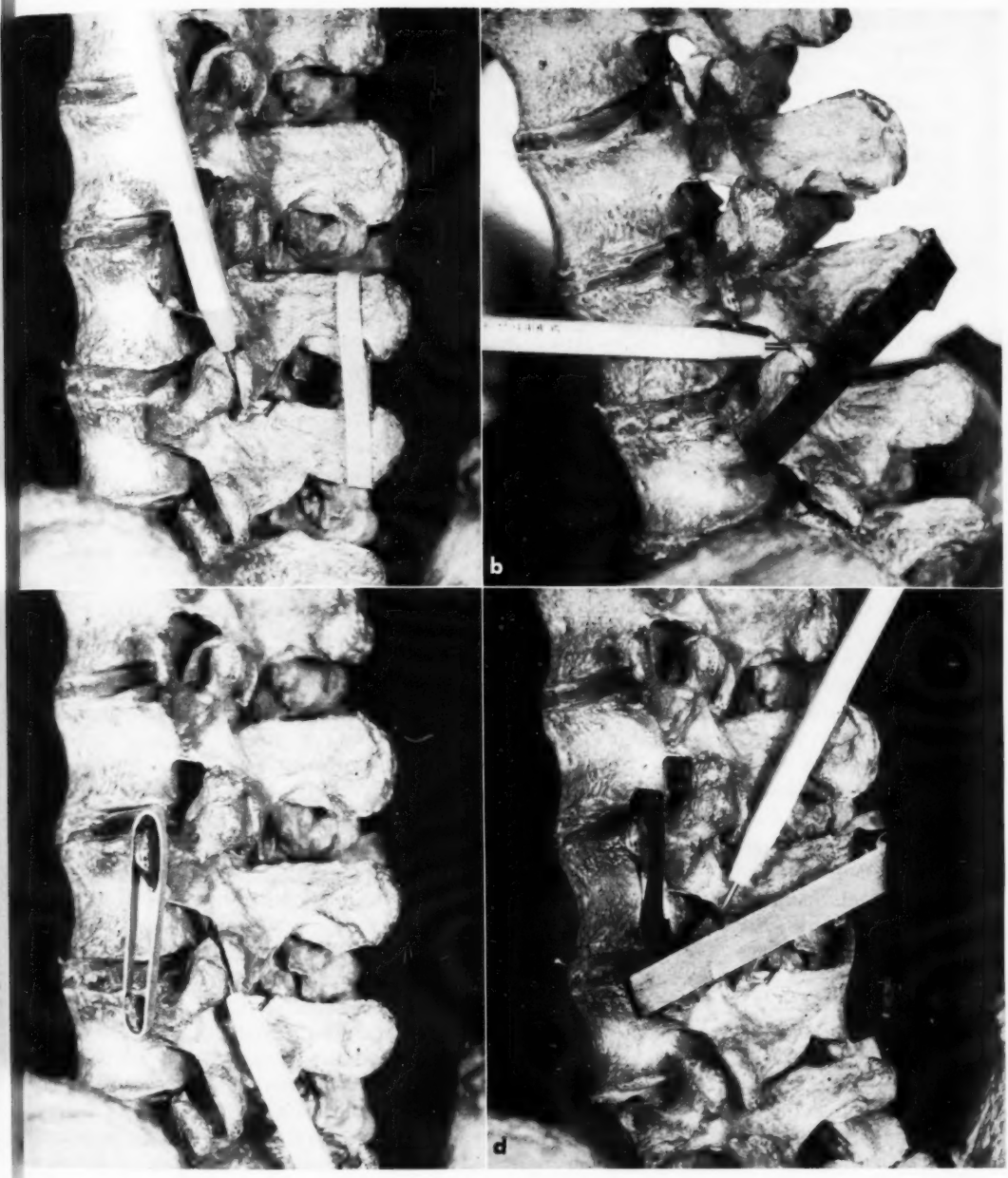


FIGURE 4a. Representation of action of spinalis muscle and interspinous ligament by band. Pen points to facet joint.

b. Representation of action of multifidus muscle by band. Pen points to facet joint.

c. Representation of action of transversalis muscle by band. Pen points to facet joint.

d. Representation of action of myoligamentous system by the three bands. Pen points to facet joint.

The sprung back can cause local and peripheral pain. This is in keeping with the work of Kelgren,[2] who showed that noxious stimulation of the spinal appendages and associated ligamentous structures can cause the sensation of pain in more distal regions. The sprung back itself cannot be seen, but its derivative effects can be observed, i.e., tenderness at the interspinous space and long-muscle spasm or malfunction in motion. The malfunction may be limited, as can be seen when a patient with a "subacute" back tries to return to an erect position from a forward flexed state. The lower back must be stabilized so that other muscles, the gluteal and hamstring muscles, can erect the spine by rotating the pelvis upward. If the fulcrum system is inadequate the action of the erector spinae system will be off. There will be a "catch" on rising up—the erector system will overcontract, overcompensate, to provide the stabilization of the lower back. When the erect position is reached, there is a passive stabilization effect achieved by the position, and the spasm, which may have engendered a transient scoliotic configuration, will disappear.

A maintained sciatic scoliosis is the extreme example of attempted segmental stabilization by the long muscles. When the patient is prone and there is no need for segmental stabilization, the scoliosis disappears unless the inflammatory process is so severe that involuntary splinting is maintained.

(The anthropomorphic or volitional properties employed in description of muscle action are for ease of explanation.)

The phenomenon of a sprung back can occur at any level of the lumbar spine. For mechanical reasons, it is more common at L5-S1 and L4-L5, the region of greatest stress. If derangement is mild without serious muscular or ligamentous damage, the condition can clear spontaneously; but if the symptoms reflect a serious myoligamentous inadequacy it is necessary to determine the level of derangement to serve as a guide to further diagnosis and treatment.

The sprung back may present several areas of tenderness. Usually there is a primary area of instability which can be observed by the marked tenderness at the interspinous space. Adjacent interspinous spaces sometimes exhibit tenderness of a lesser intensity, a reflection of abnormal demands placed on contiguous intervertebral joints.

For accurate determination of the primary unstable level we use the injection of hydrocortisone into the interspinous space. This gives a prolonged anti-inflammatory action. This effect is of sufficient duration, in contradistinction to that of local anesthetic agents, to permit the secondary manifestations in the adjacent joints and associated musculature to subside. In many cases, sufficient relief is obtained to give the injection therapeutic as well as diagnostic significance. This often permits treatment to be given on an ambulatory basis and avoids the muscular weakness and subsequent decompensation that often result from prolonged bed rest.

Functional Clinical Classification

We divide back disability according to the following functional clinical classification:

A. *Acute sciatic scoliosis*—Severe spasm of the erector spinae system, usually with a shift of the trunk in the erect position; peripheral pain may be present, but there are no objective neurologic findings. (A positive straight leg-raising test is not alone considered a neurologic finding.)

Projected functional pathology—An acute asymmetric inadequacy of the stabilization mechanism at one level with marked attempted compensatory spasm of the erector group.

B. *Low back pain with peripheral radiation; negative neurologic findings*—The absence of erector spinae spasm severe enough to cause marked fixed postural abnormality differentiates this category from group A.

Projected functional pathology—The segmental stabilization mechanism is not quite adequate and is strained by ordinary normal functional demands. This strain of myoligamentous structures whose capacity is limited because of inherent inadequacy causes both local pain and referred pain.

C. *Low back pain with peripheral radiation; positive neurologic findings*—This is the group in which it was considered that periph-

eral pain was based on a compressive radiculopathy caused by a herniated disk.

Projected functional pathology—The deranged mechanics of faulty stabilization lead to attrition of the annulus fibrosus and posterior longitudinal ligament. This leads to a herniation of the intervertebral disk. In some cases, the strain of normal stabilization in the presence of a developmental inadequacy of the disk-supporting structures is the cause of its protrusion.

D. *Chronic low back pain*—This is a perceptibly older group than the foregoing. In general, peripheral radiation has not been an outstanding feature.

Projected functional pathology—There is a chronic inadequacy because of atrophy and replacement of the small muscle-ligament system by scar tissue which cannot stand the stress, or arthritic joints which cannot take the stabilization forces of the small muscle-ligament system.

These categories are relevant to the concept of the sprung back because they present varying degrees of derangement of the small muscle-ligament system in the stabilization mechanism. It will be noted that the classification is purely clinical. An x-ray is important to rule out causes of back disability other than a myoligamentous derangement, and gives evidence of previous difficulties but often little clue to the present locus of irritation which is basically soft-tissue pathology. An x-ray can indicate pain potentialities but is rarely the direct representation of pain actualities. It is most often a record of the past. Such anatomic criteria as facet asymmetry may be the basis for derangement of the short muscle-ligament system by imposing unusual wear and tear for the demanded range of motion. A narrowed intervertebral space is the result of unnatural strains imposed on the fulcrum mechanism. Functional criteria such as straightening indicate secondary muscle spasm of the erector group. Increase of the lumbosacral angle is a reflection of strain rather than a cause.

Discussion

When the proper interspinous space is injected with hydrocortisone the usual response is some improvement within the first few minutes. Improvement is sustained or diminished somewhat in the next several hours. The next day brings a more definitive response. Approximately 10 per cent of patients have an increase in local pain after six hours, which lasts up to 12 hours. Injection of hydrocortisone in the proper interspinous space usually relieves the derivative muscle spasm of sciatic scoliosis in a dramatic fashion. Relief of the intrinsic muscle spasm as a primary procedure may permit realignment of the acutely deranged stabilization mechanism, the derangement having been maintained by the secondary spasm of the long muscles. Although the lumbosacral space is the seat of difficulties in the majority of cases, at least 40 per cent are above this level. Often the apex of the curve, the interspace that presents greatest tenderness, is as high as the 12-13 space.

There is much documentation of relief of this condition through many means, ranging from ethyl chloride spray to muscle relaxants. None of the success of these modalities would contravene the explanation that the basic derangement exists in the short muscle-ligament system.

Group B contains the cases in which the poor segmental stabilization affects the musculature concerned with erecting the trunk and maintaining stabilization for motion. In addition, peripheral pain sensation can be accounted for by stimulation of the paraspinal connective-tissue structures. The action of hydrocortisone in relieving pain indicates that these disturbances are accompanied by an inflammatory reaction which of itself augments dysfunction.

In group C, cases in which there are positive neurologic findings, there usually is good relief of the back component but moderate or only partial transient relief of the extremity pain. This makes the injection appealing as an indicator of pain from continuing root pressure as opposed to pain on a referred basis. It is useful in differentiating group B from group C. The peripheral relief, if forthcoming, takes place in 24 to 72 hours. Two explanations can be applied to this. One is that the hydrocortisone permits some realignment of the verte-

bral body relationship by allowing "unlocking" of the intrinsic mechanism. The other is that the hydrocortisone, not held fixed as in an intact joint, can migrate to the dural sleeve region. Here it acts on the nerve root structure still manifesting irritation even though the initial pressure mechanism is no longer operative. Although pain may be relieved with this maneuver, the objective neurologic findings usually resolve slowly.

Although relief is often obtained in chronic backache, additional measures usually are necessary to control recurrence. These include an exercise program, heel lifts to offset difference in leg length, and low back supports to aid in stabilization.

The response to the injection in terms of degree and persistence of relief is of value in quantitation of the derangement. Localization of the derangement is important if its nature is such that surgery is contemplated. A fusion beyond the confines of the affected area demands greater compensatory measures of the remaining joint units. This added stress may strain the supporting structures beyond their capacity, and further derangement may result.

Conclusion

The myoligamentous system of the back has two basic functions: segmental stabilization and movement of the stabilized segments as a group. Stabilization is brought about by the intrinsic or small muscle-ligament system acting on the intervertebral joints. Gross motion then is brought about by the long muscles that span more than one intervertebral space. Derangement of the small muscle-ligament system (sprung back) can cause local and peripheral pain. Access to the intrinsic system with a needle can be obtained through the interspinous space. Injection of hydrocortisone in this space will permit localization of the affected level and give some idea of the degree of derangement. In addition, the injection can help differentiate pain of continuing root pressure from referred pain of a sprung back.

REFERENCES

1. Newman, P. H.: Sprung back. J. Bone & Joint Surg. 40:32, 1952.
2. Kelgren, J. H.: On the distribution of pain arising from deep somatic structures. Clin. Sc. 4:35, 1939.

MEETINGS *and Postgraduate Courses*

Second International Meeting of Forensic Pathology, New York: To be held September 18-21, 1960. Meeting will include dedication of the new building for the Office of the Chief Medical Examiner, City of New York. For further information, write to: Dr. Milton Helpern, 55 East End Avenue, New York 28; Dr. Charles Larsen, Tacoma General Hospital, Tacoma 5; or Dr. Francis E. Camps, 37 Welbeck Street, London W.1, England.

University of Kansas School of Medicine: Postgraduate courses for 1959-1960.

Offered in conjunction with the Neosho County Medical Society, at the Southeast Kansas Tuberculosis Hospital, Chanute:

- What antibiotic should I use?, December 15
- Early depressive reactions: Diagnostic problem in general practice, January 19
- Physiologic approach to understanding heart disease in children, February 16
- Changing concepts in thyroid metabolism, March 15
- Plastic cosmetic surgery, April 19

For further information, write to: Department of Postgraduate Medical Education, University of Kansas School of Medicine, Kansas City 12.

Offered in conjunction with the Missouri Academy of General Practice, Northwest Missouri Chapter, at the Moila Temple, St. Joseph:

- Resistive heart-failure, December 15
- Medical management of ulcerative colitis, January 19
- Dietetic prescriptions, February 16
- Evaluation of the anemic patient, March 15
- Early depressive reactions: Diagnostic problem in general practice, April 19
- What antibiotic should I use?, May 17

For further information, write to: Dr. John P. Mabrey, Plattsburg, Missouri.

University of Oklahoma Medical Center, Oklahoma City: Postgraduate courses for 1959-1960:

- Renal diseases in childhood, December 9
- Carl Puckett memorial lecture and infectious diseases symposium, January 13
- Rehabilitation of the cardiac patient, February 10
- C. B. Taylor lectureship and urology symposium, March 9
- Anesthesia for the part-time anesthetist, April 13
- Neurologic diseases in childhood, May 11
- Practical considerations of neurosurgical problems, June 8

For further information, write to: Office of Postgraduate Education, University of Oklahoma Medical Center, 800 N. E. 13th Street, Oklahoma City 4.

Scientific Exhibit

The Modern Endocrine Approach to the Management and Diagnosis of the Infertile Patient

Herbert S. Kupperman
Jeanne A. Epstein
Meyer H. G. Blatt
Abraham Stone

New York University-Bellevue Medical Center and the Margaret Sanger Research Bureau, New York City

A STUDY of the infertile couple demands a definitive diagnosis, wherever possible, to delineate the most effective therapeutic approach, the ultimate prognosis, or both. Newer advances in endocrinology provide effective tools for clarifying previously unclassified problems in the infertile couple.

This exhibit presents a simplified, schematized plan of study of the aberrant physiology of the glands of internal secretion and their subsidiary organs: pituitary gland, thyroid gland, adrenal glands, ovaries and uterus, testes and penis.

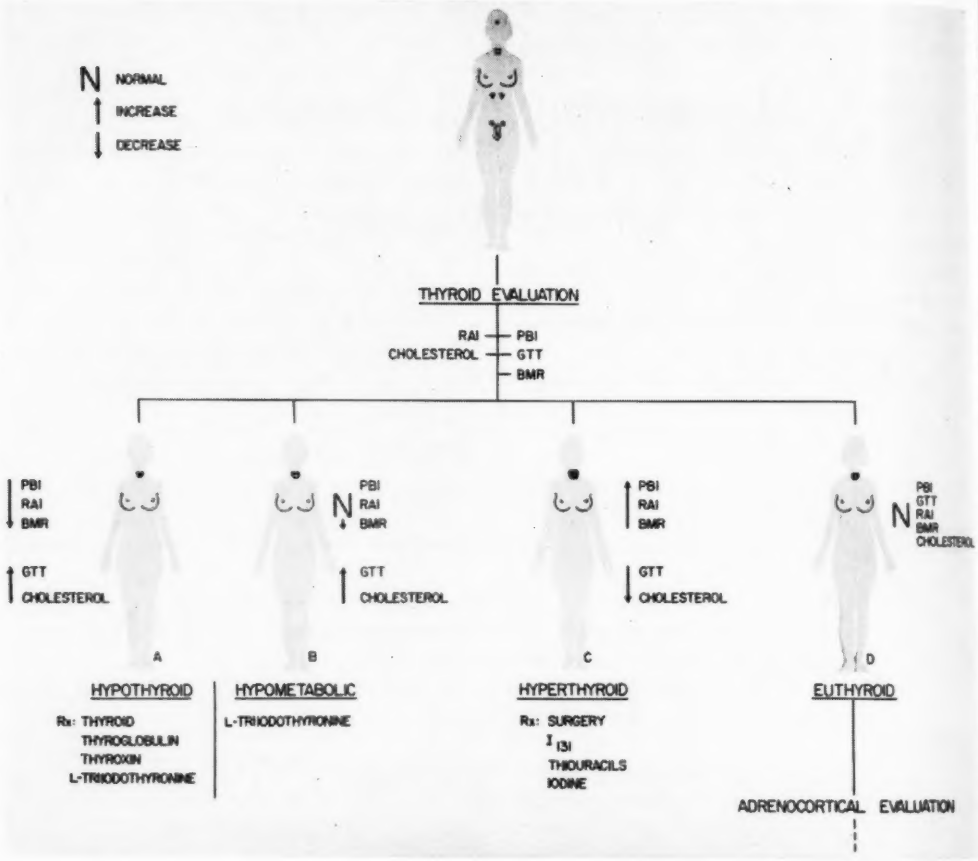
In the absence of obvious obstructive phenomena to conception, one may categorize the diagnostic and therapeutic approach according to the following classification:

Medically correctable disorders

Surgically correctable disorders

Irremediable infertility

Adapted from an exhibit presented at the annual meeting of the American Medical Association, New York City.



Thyroid evaluation in the infertile female. Diagnostic findings and therapy. (PBI, protein-bound iodine; RAI, radioiodine uptake; GTT, glucose tolerance test.)

Infertility due to faulty production or utilization of thyroid hormone

Classic hypothyroidism and hyperthyroidism usually present no diagnostic or therapeutic problems as related to sterility, but infertility often may be the only or earliest manifestation of either *incipient hypothyroidism* or the *hypometabolic syndrome* (euthyroid hypometabolism, nonmyxedematous hypometabolism, metabolic insufficiency, pseudohypothyroidism).

Clinical and laboratory diagnostic findings in hypothyroidism and the hypometabolic syndrome

Clinical findings (usually not striking)	Ovulatory defects Oligospermia with or without diminished sperm motility Fatigue Dryness of skin (extensor surfaces most marked) Cold intolerance

Laboratory tests	*Hypothyroidism*	*Hypometabolic syndrome*
Protein-bound iodine	Low	Normal
Radioiodine uptake	Low	Normal
Basal metabolic rate	Low	Low
Glucose tolerance test	Increased (flat)	Increased (flat)
Cholesterol	Elevated	Elevated
17-Ketosteroids	Low	Low

An additional diagnostic test for both hypothyroidism and the hypometabolic syndrome, applicable in children, is x-ray evidence of retardation of bone age.

Treatment

Crystalline thyroid preparations currently available offer advantages of constancy of preparation and predictability of effect. Two such compounds now widely used are sodium levothyroxine and L-triiodothyronine (liothyronine). The following chart compares doses of these compounds with equivalent doses of standard thyroid preparations.

PRODUCT	AVERAGE MAINTENANCE DOSE	TIME REQUIRED FOR FULL THERAPEUTIC EFFECT	TIME FOR DISSIPATION OF ACTION
Thyroid extract U.S.P.	100 mg.	2 to 3 weeks	2 to 3 weeks
Thyroglobulin	100 mg.	2 to 3 weeks	2 to 3 weeks
Sodium levothyroxine	0.3 mg. (300 μg.)	2 to 3 weeks	2 to 3 weeks
L-triiodothyronine (liothyronine)	0.1 mg. (100 μg.)	2 to 3 days	2 to 3 days

L-triiodothyronine has the advantage of rapid establishment of therapeutic benefits as well as relatively rapid dissipation of effect, an important aspect where toxicity supervenes.

Hypometabolic syndrome

The hypometabolic syndrome, which is comparatively common, may be overlooked because of a low index of clinical suspicion. It is thought to result from a defect in utilization of thyroid hormone at the cellular level. This defect is characterized by an inability of the tissue enzymes to deiodinate thyroxin to L-triiodothyronine. L-triiodothyronine, not thyroxin, is considered to be the thyroid hormone effective peripherally in cellular metabolism; therefore, it is the logical replacement therapy in the hypometabolic syndrome. Response to treatment includes restoration toward normal of gonadal function tests, rise in basal metabolic rate, decrease in elevated serum cholesterol levels, and normalization of glucose tolerance.

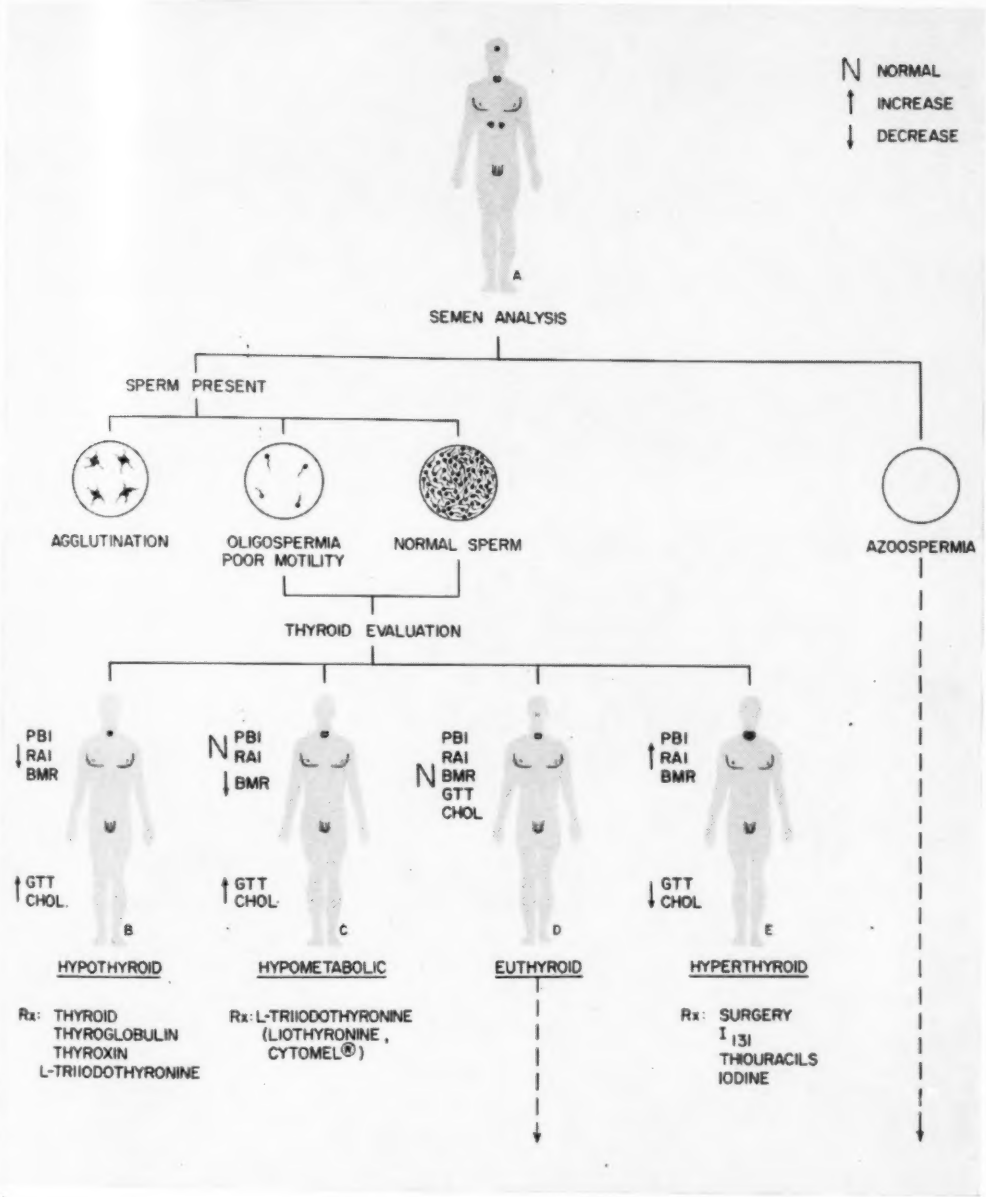
Sperm agglutination

Spontaneous immobilization of spermatozoa by clumping due to uninhibited agglutinins is a relatively rare phenomenon which has recently proved amenable to treatment. Sperm agglutinins are normally present, as are antiagglutinins. The latter have been shown to be inactive in the oxidized state and can be activated in vitro with any suitable agent. An effective reducing agent which has been shown to accomplish this in vivo is ascorbic acid, 100 mg. t.i.d.

Oligospermia

Physiologically it has been shown that follicle-stimulating hormone is the trophic principle necessary for spermatogenesis. Pregnant mares' serum (EQUINEX®), 500 I.U. t.i.w. for three weeks, has, primarily, follicle-stimulating hormone activity and may be used to enhance spermatogenesis in patients with a paucity of spermatozoa in the semen. It must be emphasized that the course of therapy should be limited to two months due to the foreign-protein nature of the substance and its propensity to cause antihormone production in the human. Supplementation of pregnant mares' serum with androgens during the latter half of the course of therapy may further stimulate spermatogenesis.

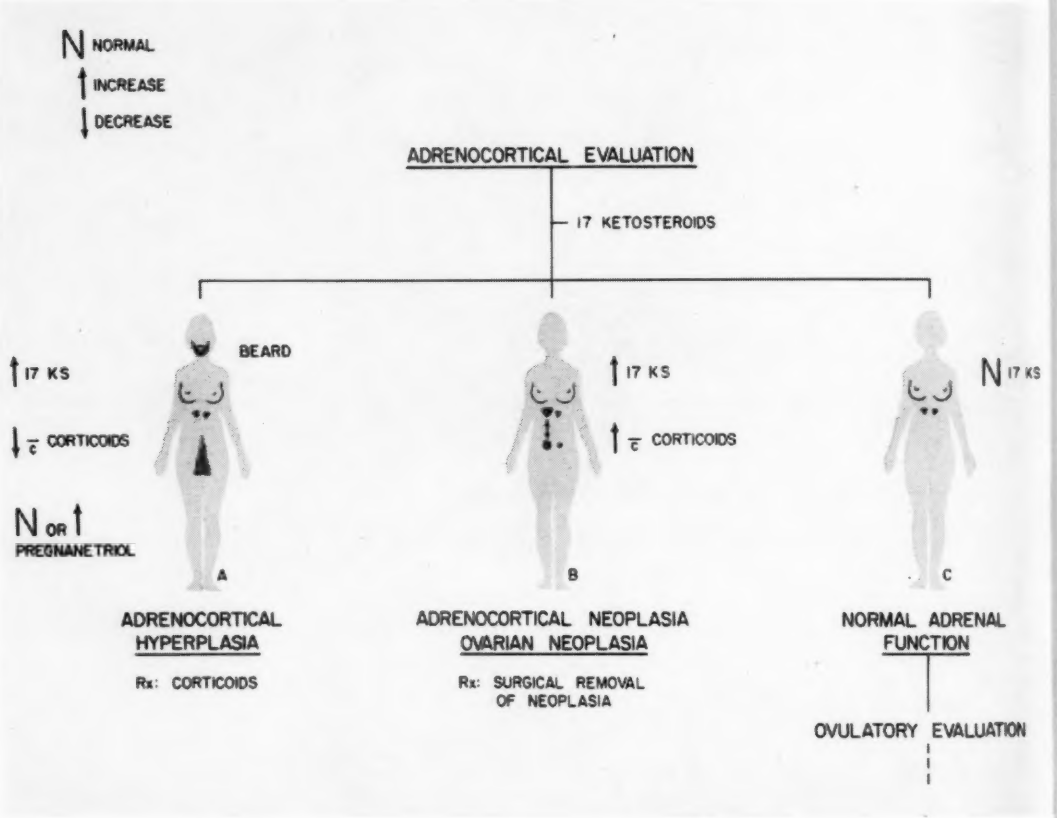
Seminal fluid defects



Evaluation of seminal fluid potential and thyroid function in the infertile male.

Adrenal hyperplasia–adrenogenital syndrome (AGS)

Because of the androgenic potential of adrenal steroid synthesis, gonadal dysfunction secondary to pituitary gonadotropic inhibition may range from complete gonadal inhibition to suppression of gametogenesis. Clinical manifestations vary in severity depending on the congenital or postpuberal nature of the disease.

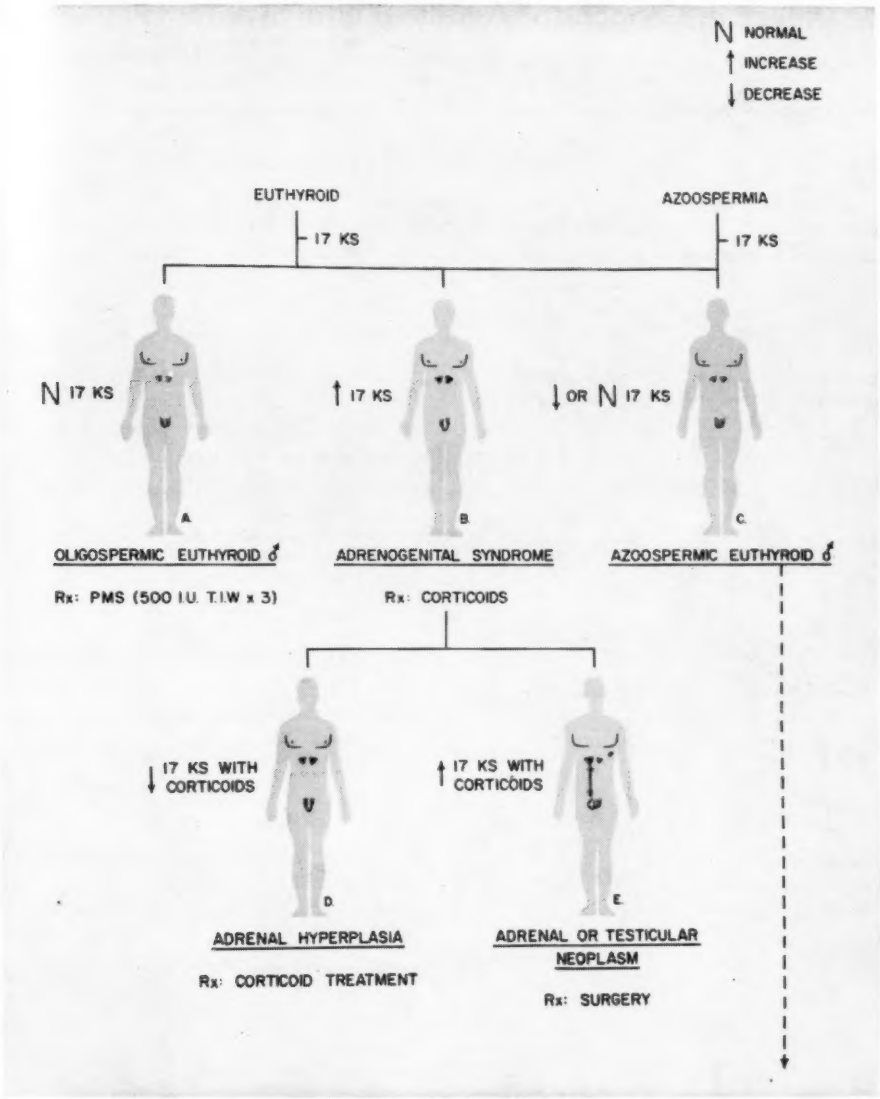


Adrenocortical evaluation in the infertile female. Diagnostic findings and therapy.

Diagnosis

Clinical

Male	Female
Enlarged penis	Hirsutism, none to 4 plus
Small testes	Clitoral enlargement, none to 4 plus
Oligospermia to azoospermia	Normal to hypoplastic breasts
	Normal feminine to masculine habitus
	Anovulatory basal body temperature curve
	Normal to castrate vaginal smear



Adrenocortical evaluation in the infertile male. Diagnostic findings and therapy. (PMS, pregnant mares' serum.)

Biochemical

Elevated 17-ketosteroids

Normal to low 17-hydroxycorticoids

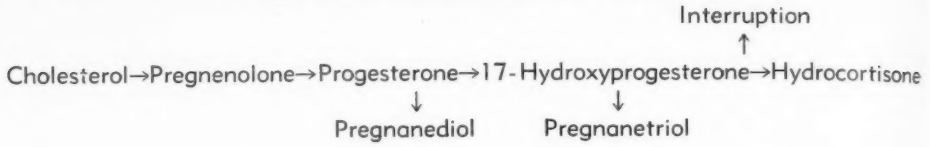
Normal to elevated pregnanetriol

Therapeutic response to corticoids

Decrease in 17-ketosteroids and pregnanetriol on physiologic doses of corticoids

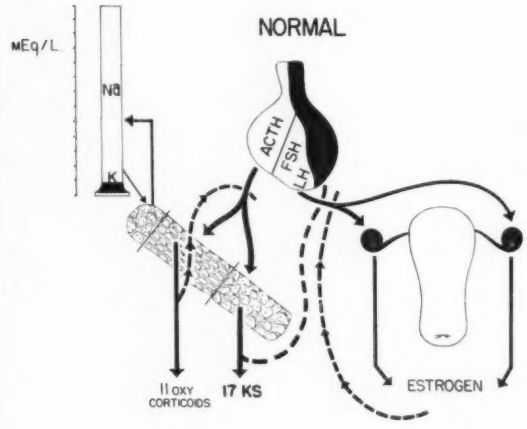
Appearance of biphasic basal body temperature chart

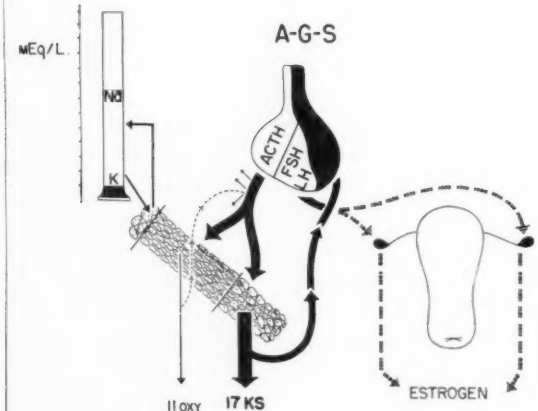
Basic Defect in Congenital Adrenogenital Syndrome

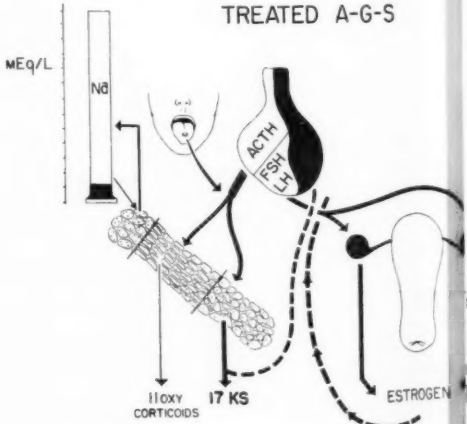


Interruption of the formation of hydrocortisone leads to excess excretion of pregnanediol and pregnanetriol accompanied by increased production of androgenic (virilizing) adrenal steroids.

Pituitary-adrenocortical-ovarian axis: normal, adrenogenital syndrome, and treated adrenogenital syndrome.







Treatment

The postpuberal type responds to physiologic doses of the corticoids in a comparable manner. The average doses of the available corticoids used in treatment are:

Cortisone, 12.5 mg. t.i.d.
Hydrocortisone, 10 mg. t.i.d.
Prednisone, 2.5 mg. t.i.d.
Prednisolone, 2.5 mg. t.i.d.
6-Methyl prednisolone, 2.0 mg. t.i.d.
Triamcinolone, 2 to 3 mg. t.i.d.
Dexamethasone, 0.375 mg. t.i.d.

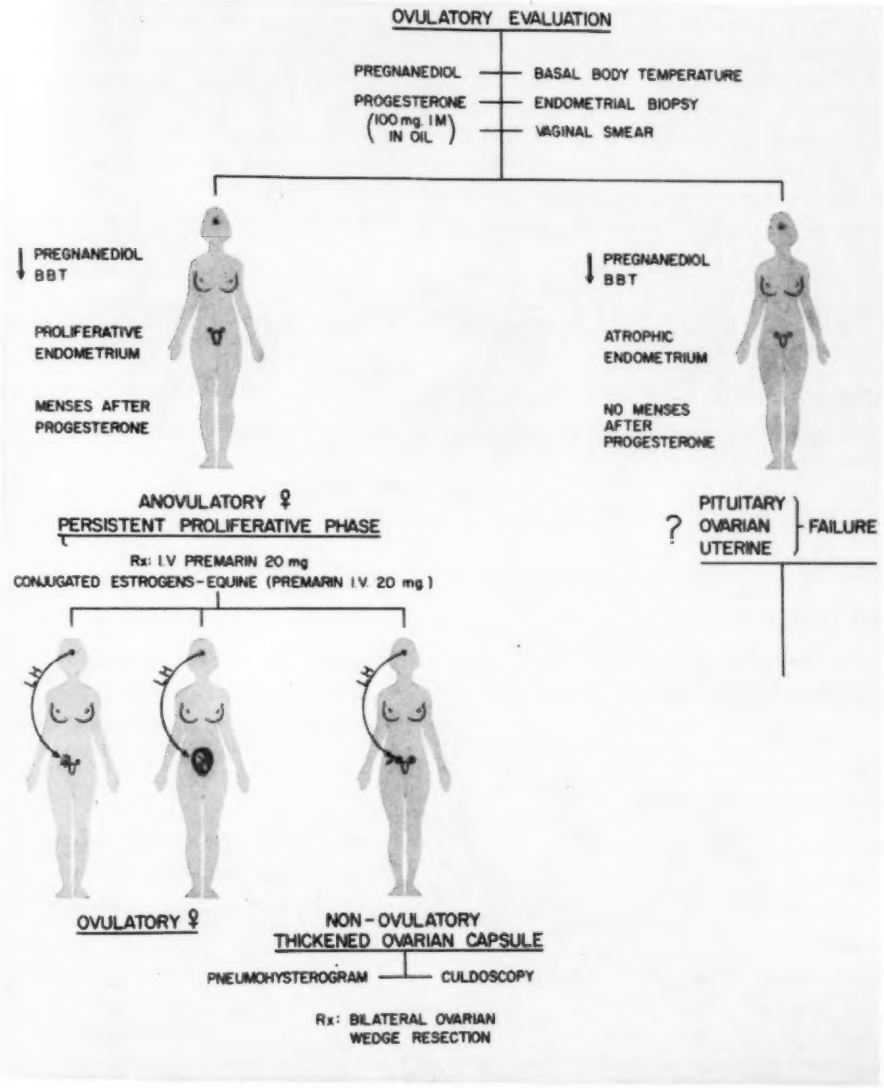
The optimal therapeutic dose is the *minimal* dose which will:

1. Depress 17-ketosteroids and pregnanetriol to normal levels.
2. Initiate menarche in congenital adrenogenital syndrome.
3. Restore ovulatory menses in postpuberal adrenogenital syndrome.

Note: Hirsutism usually is not changed until after 9 to 12 months of effective therapy, if it is changed at all. Clitoral enlargement is unalterable.

Ovulatory failure due to pituitary-ovarian imbalance

Experimental evidence has shown that ovulation requires the release of luteinizing hormone from the pituitary. Its release depends on an adequate estrogen level.



Ovulatory evaluation in the infertile female. Diagnostic findings and therapy.

Treatment

Ovulatory failure, due to defects in the above mechanism, may be corrected by rapid adjustment of the estrogen level to that necessary for the release of luteinizing hormone. This is accomplished by intravenous administration of 20 mg. of conjugated estrogens equine, PREMARIN®.

Response to Intravenous Conjugated Estrogens Equine

PATIENTS	OVULATORY		NONOVULATORY (FOLLICULAR CYSTIC OVARIES)		UNDETERMINED (INADEQUATE FOLLOW-UP)
	Number of Patients	*Number Pregnant*	*Number of Patients*	*Dx Confirmed by Surgery*	
Infertility cases	13	6*	9	4†	2
Others	3	0	6	1	2
Totals	16	6	15	5	4

*Average duration of infertility 4.3 years (range two to seven years).

†One patient became pregnant after bilateral ovarian wedge resection and a nine year history of infertility.

SURGICALLY CORRECTABLE DISORDERS

Follicular Cystic Disease of the Ovary (Stein-Leventhal Syndrome)

This disorder is one of a mechanical barrier to ovulation because of the thickened, fibrotic ovarian tunica.

Diagnosis

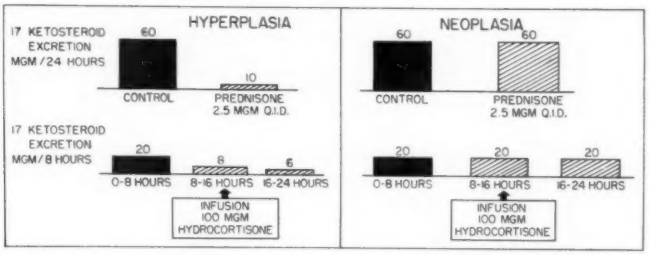
Early clinical picture	Clinical and laboratory tests
Normal, eumorphic female	Menses after progesterone alone
Monophasic basal body temperature curve	Cornification of vaginal smear
	Normal thyroid and adrenal parameters
Advanced clinical picture	
Obesity	Normal thyroid and adrenal parameters
Hirsutism	Response to progesterone positive or negative*
Breast atrophy*	Normal or castrate vaginal smear*
Amenorrhea	
Hypertension	
Large, palpable ovaries	

*In advanced cases, signs of estrogen deficiency may occur as a result of pressure necrosis of the enlarging cysts on the ovarian parenchyma.

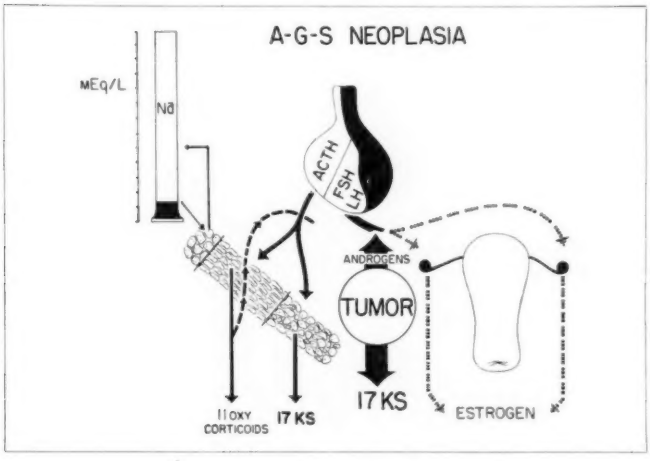
A critical diagnostic test in either early or advanced disease is failure of an ovulatory response to the intravenous administration of 20 mg. of conjugated estrogens equine (Premarin). This test is a useful tool for diagnosing those patients who do not show any of the advanced stigmata of the disease.

Neoplasm of adrenals or gonads

The relatively sudden appearance of menstrual abnormalities and masculinization in a previously normal menstruating female should alert the physician to the possibility of a neoplasm of the adrenals or ovaries; 17-ketosteroid excretion may be normal or elevated. Normal 17-ketosteroid levels, in the presence of the above symptoms, should lead to suspicion of either an arrhenoblastoma or a luteoma. However, elevated 17-ketosteroids have been found in a few cases of arrhenoblastoma. Elevated 17-ketosteroids with these symptoms would indicate adrenal neoplasms, adrenal rest tumors of the ovaries, or testicular tumors. Failure of oral or parenteral corticoids to depress 17-ketosteroids to normal levels before surgery is a useful diagnostic aid in determining the presence of a neoplasm.



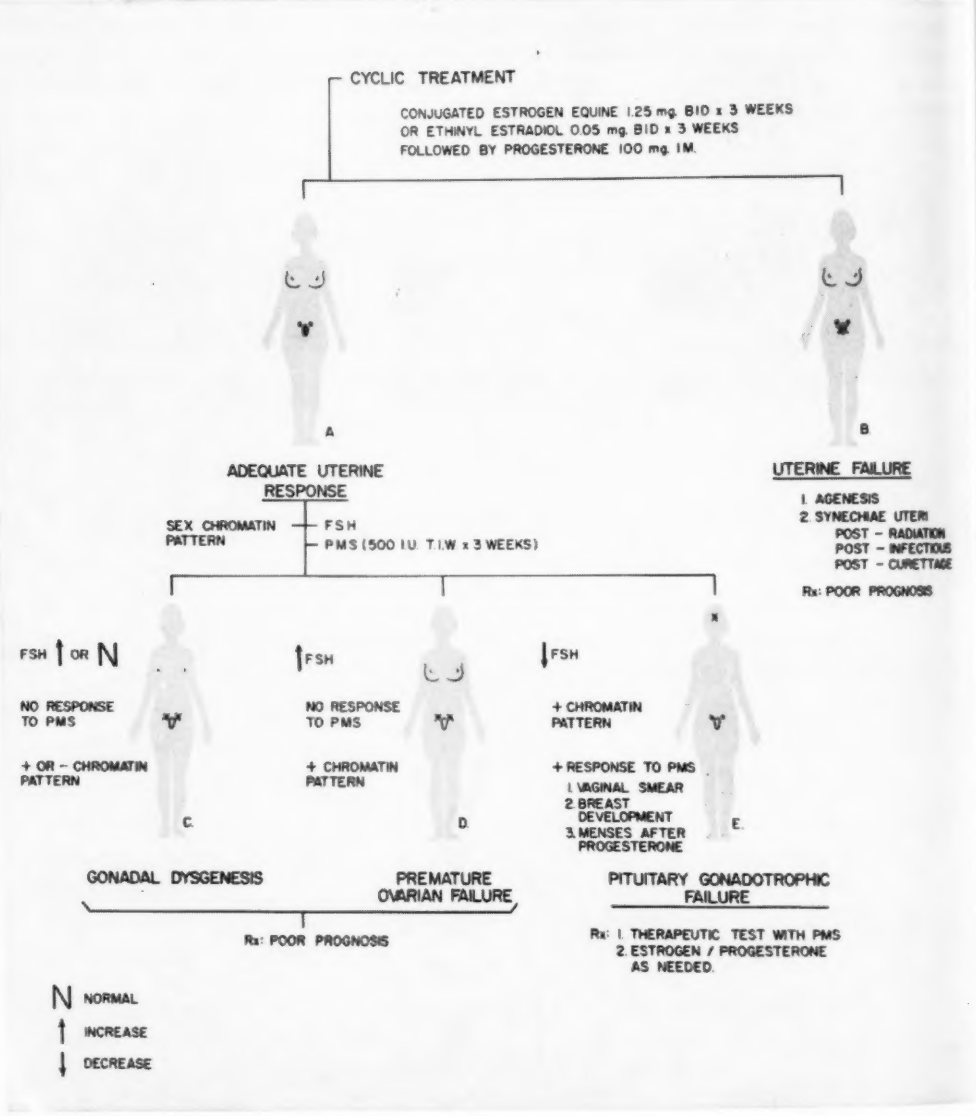
Differential diagnosis of neoplasia versus hyperplasia in adrenogenital syndrome. After surgical removal of the neoplasm, 17-ketosteroid levels and gonadal function return to normal.



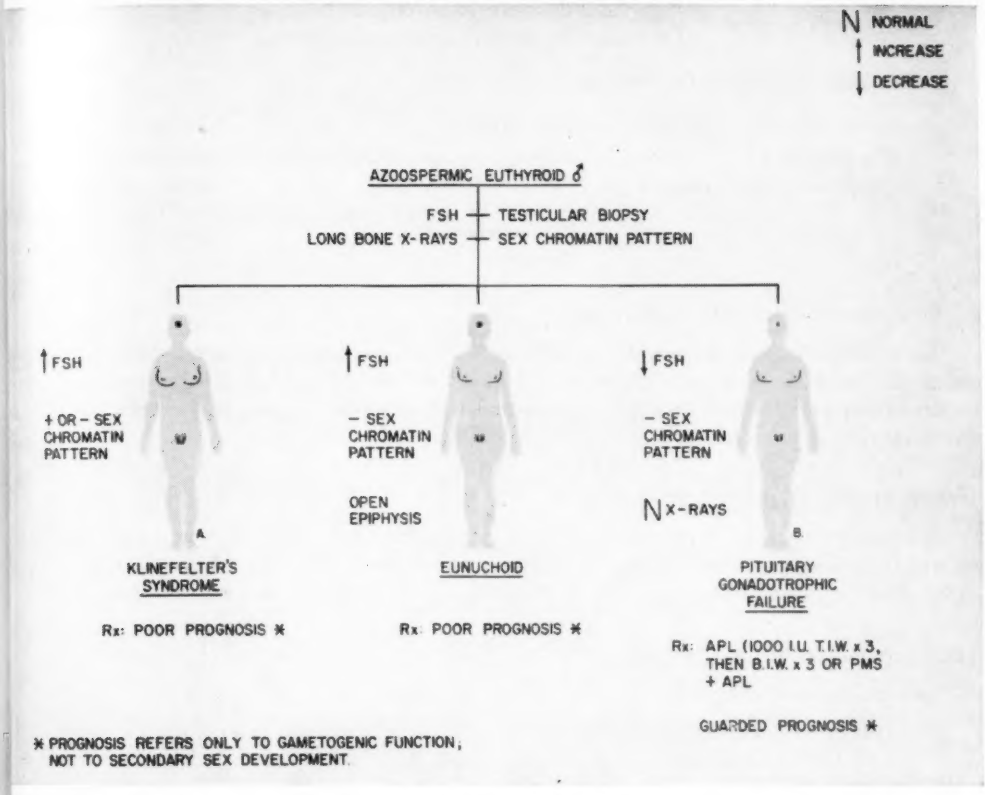
Pituitary-adrenocortical-ovarian axis.

IRREMEDIABLE INFERTILITY

Patients in this category bear a hopeless prognosis for fertility and should be so advised.



Evaluation of pituitary, ovarian or uterine failure in the infertile female.



Evaluation of testicular or pituitary failure in the infertile male. (APL, chorionic gonadotropin.)

Gonadal dysgenesis or agenesis

Turner's syndrome { gonadal dysgenesis-chromatin negative
ovarian agenesis-chromatin positive

Clinical and diagnostic findings

Anatomic

Short stature
Webbed neck
Cubitus valgus
Congenital heart disease
Pretibial lymphedema
Clitoral enlargement
Lack of secondary sex characteristics
  Aplasia of breasts
  Scant or absent axillary or pubic hair
Absence of ovaries

Histologic

Negative sex chromatin pattern in half the patients (pattern normally positive in females and negative in males)
Atrophic vaginal smear with negative response to pregnant mares' serum (Equinex)
Failure of response to progesterone alone
Menstruation following estrogen-progesterone therapy

Chemical

High or normal FSH
Normal thyroid and adrenal parameters

Once the diagnosis is established, it is important to initiate cyclic therapy with estrogens and progesterone to prevent the progerialike characteristics that these patients may show when deprived of estrogens.

Klinefelter's syndrome { gonadal dysgenesis-chromatin positive / gonadal dysplasia-chromatin negative

Clinical and diagnostic findings

Anatomic	Histologic	Chemical
Gynecomastia	Positive or negative sex chromatin pattern	High FSH
Normal to eunuchoid stature	Azoospermia	Normal 17-ketosteroids
	Tubular hyalinization	Normal thyroid and adrenal parameters
	Mazoplasia	

Prepuberal Klinefelter's syndrome

Early diagnosis may be established only on the basis of histologic characteristics plus a high index of suspicion. Histologic characterization is based on the peritubular fibrosis noted in testicular biopsy and the positive chromatin pattern seen in some patients; replacement therapy begun early may circumvent some of the undesirable anatomic abnormalities.

Premature ovarian failure

Idiopathic cessation of previously normal ovarian function, a high urinary gonadotropin level, and failure of response to pregnant mares' serum are characteristic of this disorder. Premature "progeria" should be avoided by cyclic therapy with estrogen and progesterone.

Inflammatory processes

Tuberculous endometritis

Diagnosis is established by endometrial biopsy and by failure of menses to occur when cyclic therapy with estrogen and progesterone is instituted.

Viral

Mumps orchitis and oophoritis. Diagnosis is based on history of *postpuberal* infection, gonadal biopsy, azoospermia and evidence of ovarian failure.

Postradiation infertility

Therapeutic

Destruction of endometrium because of uncontrollable uterine bleeding, i.e., polyps, submucous fibroids, and endometrial hyperplasia. Diagnosis is established by history, failure of response to cyclic therapy with estrogen and progesterone, hysterogram, and absence of tissue on curettage.

"Stimulation"

Promiscuous use of "stimulating doses" of x-ray to the pituitary and ovaries has resulted in permanent ovarian failure in some patients. Diagnosis is established by a history of radiation therapy, high FSH, or absence of measurable gonadotropin excretion and failure of menses to occur with progesterone alone.

Adventitious irradiation

Roentgenologists, technicians and excessive diagnostic x-rays in patients (theoretical).

Mechanical destruction of endometrium

Curettage for postpartum hemorrhage or incomplete abortion may result in complete removal of endometrium with ultimate obliteration of uterine cavity.

Therapeutic Approaches Toward Control of Hypercholesteremia

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In 1843, Vogel identified cholesterol in atheromatous arteries, and in 1910, Windaus showed that these deposits are present in the form of cholesterol esters. The relationship of this metabolite to atherosclerosis became apparent a couple of years later when studies from at least four European laboratories demonstrated that this disease can be experimentally produced in rabbits fed diets containing cholesterol. Since then, literally tons of cholesterol have been offered to several species by numerous investigators, and almost without exception, if the dietary conditions were sufficiently severe, atherosclerotic lesions were induced. In almost every experimental trial the gross or microscopic appearance of these lesions was accompanied by a hypercholesteremia. However, some observers have looked on the success of such experiments with misgivings, for they argue that the serum cholesterol level is receiving an inordinate amount of attention at the expense of other, perhaps more profitable approaches. Although there may be some justification for such criticism, the most impressive and productive approach at the experimental level still requires new knowledge of how cholesterol is metabolized. For the most part, excursions into other metabolic pathways have shown promise only inasmuch as they affect the metabolism of these lipids.

LOUIS C. FILLIOS

Authoritative reviews of the dietary aspects of hypercholesteremia have appeared in these pages during the past year, and therefore such considerations will be discussed only as they pertain to the theme of this article. At this time, if one accepts much of the present thinking, dietary manipulations may prove to be beneficial in delaying and perhaps preventing the occurrence of a fatal infarct. Dietary management was useful prior to the discovery of insulin and is still useful to this day in the

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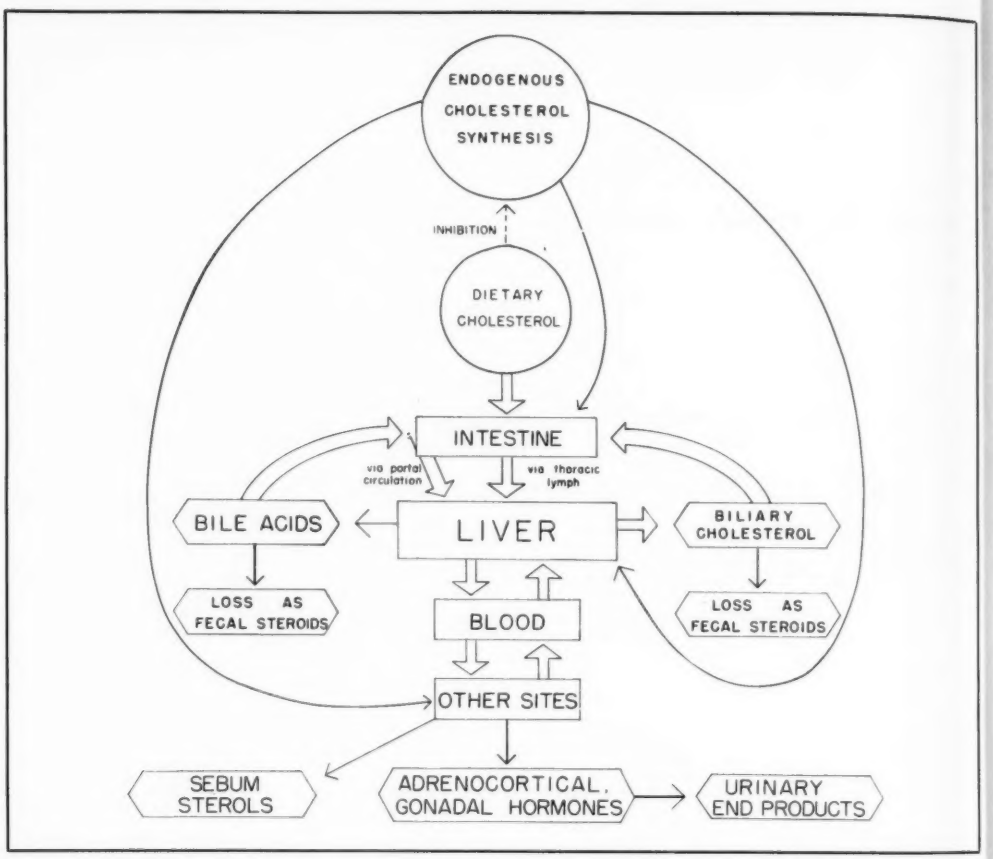

FIGURE 1. A simplified scheme of cholesterol metabolism. The solid arrows represent formation or conversion; open arrows denote transfer.

treatment of many diabetic conditions. At present, it is by far the safest approach for treating persons with hypercholesteremia when combined with competent clinical observation. Except under metabolic ward conditions, however, there are inherent weaknesses in the dietary approach. Unless patients are highly motivated and have competent nutritional advice over a long period of time, there is little likelihood that such programs will succeed. Furthermore, the patient must acquire a sufficient comprehension of practical nutrition in order to select foods which are both desirable and palatable. Finally, to add to the difficulties of this approach, there is lack of agreement among nutritionists themselves as to what constitutes the most acceptable nutritional program for maintaining a desirable serum cholesterol level.

In the present article an attempt will be made to discuss generally some of our knowledge about the importance of cholesterol metabolism and the prospects for successfully treating hypercholesteremics. Assuming that the control of cholesterol metabolism will lead to a lower incidence of coronary artery disease, let us consider what has been attempted and in this light speculate on what may be done in the near future.

Most efforts at the experimental level are still based essentially on the nutritional approach. Few investigators will disagree with the general statement that an interaction between adverse dietary habits and genetic sus-

eptibility probably accounts for a very large ercentage of atherosclerotic patients. Other ontributing factors, such as stress, physical ctivity, sex, etc., have been important conderations but, for the most part, their imortance has been evaluated in the light of hanges in the blood cholesterol fraction. For better understanding of where cholesterol elongs in the over-all scheme of things, an nderstanding of its metabolic importance is nandatory (figure 1).

Blood cholesterol is derived from two ources: dietary and endogenous. As far as we now, most higher-order vertebrates do not equire cholesterol in their diet. Yet this comound is an essential constituent and now as been shown to be synthesized in practicaly every tissue where it has been studied. Howver, the rate of biosynthesis of cholesterol aries among these tissue sites; for example, he rate in the liver or the intestinal mucosa s several times greater than that in the skeletal muscle. During the rapid growth phase of an animal, brain cholesterol is synthesized at a very high rate but once myelinization is completed, cholesterol metabolism in nervous tissue becomes negligible. In the adrenal cortex where cholesterol acts as a precursor to various adrenocortical hormones, or in the gonads where it is required for gonadal hormone synthesis, a relatively high rate must be maintained throughout life. These rates, of course, will vary and are dependent on the regulatory action of the endocrine system. Since dietary cholesterol is not an obligatory source, each tissue must synthesize its needs from some elementary metabolite. It is known that the principal and simplest precursor of cholesterol is acetate (figure 2).

Acetate is activated by combining with coenzyme A to form a high-energy linkage, namely, "active acetate" (CH_3COS: coenzyme A). Essentially, two molecules of active acetate are required to form acetoacetyl-coenzyme

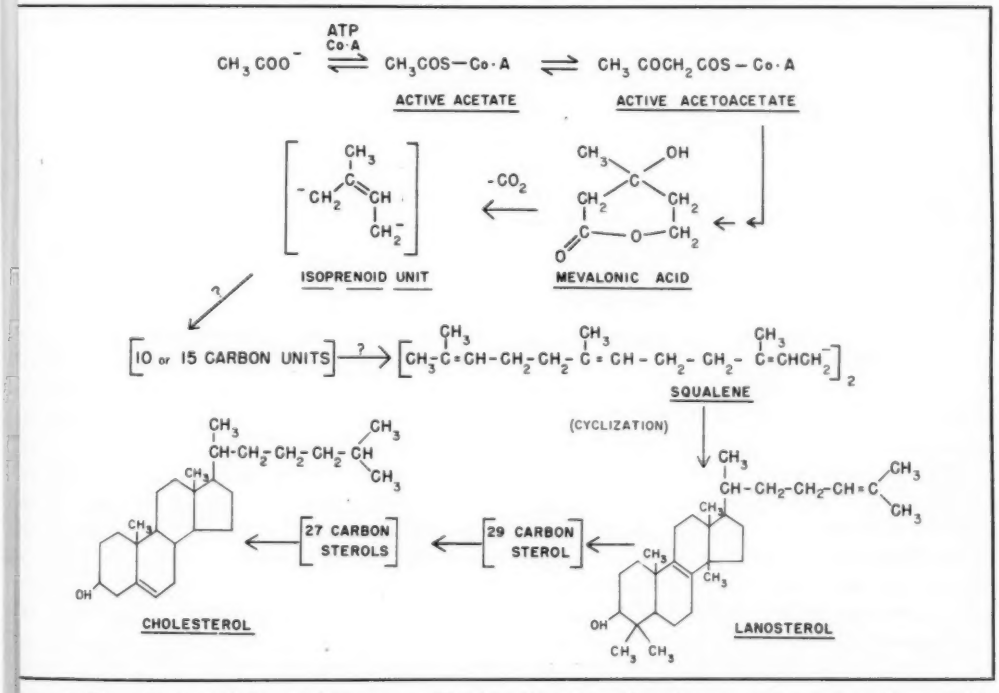

FIGURE 2. Biosynthesis of cholesterol from acetate. The formation of squalene from acetate occurs under anaerobic conditions; the squalene to cholesterol phase is believed to take place aerobically.

A (CH_3COCH_2CO-S: coenzyme A), which is a known intermediate for cholesterol, fatty acid, or ketone body formation. Although acetoacetyl-coenzyme A has been shown to be an intermediate in cholesterol biosynthesis, recent evidence indicates that an equilibrium between acetate and acetoacetate is necessary before it is made available as a precursor for cholesterol synthesis. In the same way, it has been proposed that an equilibrium between another proposed intermediate, namely, β-hydroxy-β-methyl glutarate, and acetoacetyl-coenzyme A is required prior to the liberation of the acetoacetyl into the cholesterol scheme. However, certain interrelationships in this early phase of biosynthesis still remain obscure. Several other metabolites have also been proposed, such as β-methylglutaconate, β-hydroxy isovalerate and β-dimethylacrylate, as intermediates in the pathway prior to the formation of a known six-carbon compound, namely, mevalonic acid.

Using isotopically labeled mevalonic acid, Tavormina and his co-workers found that it contributed its carbons very efficiently into the cholesterol moiety. This valuable discovery lends support to the hypothesis that a five-carbon isoprenoid unit may exist after mevalonic acid is partially degraded with a loss of one carbon. Cornforth has postulated that six mevalonic acid units give rise to each squalene molecule with a loss of six carbons as carbon dioxide. Others have postulated that a 15-carbon intermediate, similar to farnesenic acid, may exist prior to the formation of the squalene; 10-carbon intermediates related to gerantic acid have also been considered. In any event, no one has succeeded as yet in demonstrating convincingly that such 10-carbon or 15-carbon intermediates actually exist "in vivo."

Squalene, a 30-carbon triterpenoid hydrocarbon, was first isolated by Tsujimoto in 1906. This compound has now been found in mammalian tissue and has been shown to exist as an active intermediate in cholesterol biosynthesis. Understandably, the cyclization of the hydrocarbon squalene to a steroid posed a formidable task for organic chemists. Largely because of the work of Bloch and his associates, the identification of the carbon atoms of squalene in the cholesterol moiety now has been achieved. On substantial evidence, squalene first is converted to lanosterol or a similar sterol. Lanosterol loses one carbon, forming 4,4,dimethylcholestadienol or some related 29-carbon compound. Finally, via several steps, first to other 27-carbon sterols such as zymosterol and desmosterol, cholesterol is synthesized. Therefore, some known, some speculated, and some unknown intermediate metabolites exist in the acetate to cholesterol pathway. At this time, the main guideposts can be summarized as acetate ⟶ acetoacetate ⟶ mevalonic acid ⟶ 5-carbon unit ⟶ squalene ⟶ lanosterol ⟶ zymosterol ⟶ desmosterol ⟶ cholesterol.

There have been attempts to inhibit cholesterol biosynthesis as a means of lowering the cholesterol level. Before we discuss the validity of this approach, let us consider briefly what has been attempted. When either β-phenylvalerate or α-phenylbutyrate is fed to rats, cholesterol biosynthesis is partially inhibited, and the inhibition is believed to take place early in the pathway, probably in the formation of acetoacetate from acetate. Such compounds do not have much promise since an interference in fatty acid metabolism could also take place at these sites. In order to reduce cholesterol formation without interfering with other essential metabolic processes, the inhibition should perhaps be carried out farther along the pathway. Such attempts have been made. The inhibition of mevalonic acid to cholesterol has been achieved with α, ρ-biphenylbutyrate. Also an inhibition somewhere between squalene and cholesterol can be partially achieved by feeding compounds such as 7-dehydrocholesterol. Attempts with other steroid inhibitors such as Δ^7 cholestenol. dehydroisoandrosterone and cholesterone have had a modicum of success in animals. More recently, another compound, called MER-29, is believed to inhibit cholesterol biosynthesis in the rat at a stage immediately following squalene, during the stage of the closing of the steroid rings.

Granted that compounds are available for inhibiting cholesterol biosynthesis at any of

the stages outlined, of what value are they in preventing atherosclerosis? First it must be established that the endogenous synthesis of cholesterol should be controlled. It is known that, depending on the species, exogenous or dietary cholesterol to a varying degree inhibits cholesterol biosynthesis. In other words, an attempt to maintain a steady state of cholesterol equilibrium exists. The tissues create what they need. If, however, dietary cholesterol is available to fulfill these needs, then synthesis, particularly in the liver, is partially inhibited. On the other hand, if excessive dietary levels of cholesterol persist over a sufficiently long period of time, abnormal deposits of cholesterol can occur, and this situation is reflected by a hypercholesteremia. In man, a serum cholesterol level above 200 mg. per cent, although representative of the adult population of the United States, is in reality high as shown by comparisons with certain other populations of the world. Furthermore, in most other mammals, cholesterol levels of less than 150 mg. per cent are observed. Generally, only when certain dietary ingredients, including cholesterol, are introduced does hypercholesteremia occur in animals, and in some cases it may even exceed 1000 mg. per cent. Therefore, the inhibition of cholesterol biosynthesis may not always be the definitive answer, since one of the most effective ways of inhibiting cholesterol biosynthesis is to feed cholesterol or related compounds.

Another strong argument at this time against any enthusiastic clinical use of antibiosynthesizing compounds is that little is known about the significance of the different rates of biosynthesis in various tissues. Not only is cholesterol synthesized at a different rate from organ to organ, but the rate of biosynthesis may normally vary within each tissue from time to time. In effect, under normal conditions, tissue rates are both varied and variable. Therefore, the agent to be used must be highly selective. It must be known where the defect, if any, of biosynthesis resides. If it is in the liver, as many suspect, then the agent must selectively lower the biosynthesizing rate of the liver appreciably while not interfering with the essential metabolic processes of this organ. Furthermore, this regulation of hepatic and serum cholesterol must be carried out without causing serious metabolic imbalances at other tissue sites. The ultimate criterion for evaluating the efficacy of such agents demands that the disease process must be arrested or retarded.

Atherosclerosis is an insidious process, perhaps requiring several years to develop to a stage where it can be clinically detected. The experimentalist has reduced the duration of the pathogenesis by employing an exaggerated simulation of the conditions which he believes may be necessary to induce the disease. Although this approach is subject to some criticism it is still the best means available. Therefore, the attempts to treat atherosclerosis have for the most part been attempts to lower the cholesterol level of the blood, which can be accomplished in man and experimental animals in a number of ways. Perhaps the most successful approach to date has been by dietary means. Alterations of the dietary fat, supplementation of the diet with phytosterols to interfere with the absorption of cholesterol, and other dietary alterations have been tried. Also various vitamin and mineral supplements have been tried; for example, vitamin C, pantothenic acid, pyridoxine, vitamin A, vanadium, cobalt, magnesium and calcium have been implicated in various studies. Another approach is the use of drugs such as nicotinic acid and certain choleretic agents.

The value of nicotinic acid as a cholesterol-lowering agent has been confirmed. Apparently, it does not act in its capacity as a vitamin since nicotinamide, the active vitamin principle, does not have the same effect on the serum cholesterol level. It appears that nicotinic acid may have a direct pharmacologic effect. However, its value as a clinical tool requires further study and modification since it does cause certain objectionable side reactions such as peripheral vasodilation, gastrointestinal distress, pruritus and nervousness. Conceivably, interest in the cholesterol-lowering properties of nicotinic acid may lead to the development of chemically related drugs which are efficacious while free of any undesirable side reactions.

Recently, the use of choleretic agents such as gallogen has been proposed as useful for lowering the serum cholesterol level. Gallogen is the diethanolamine salt of the monoester of d-camphoric acid. It was proposed that if the bile secretion is increased, then, as a result, an increased excretion of cholesterol may take place. It is well known that the principal pathway for cholesterol excretion is via the biliary system; cholesterol is a known precursor to the formation of bile acids. Also cholesterol, as such, is found in bile and a fraction is lost during every reabsorption cycle. However, the results with choleretic agents such as gallogen are still inconclusive and conflicting.

The use of hormones in treating this disease has also been considered. Several years ago, it was recognized that men were more prone to coronary artery disease than women up to age 55. Therefore, it became apparent that the female hormone may perhaps protect against atherosclerosis. Subsequently, several reports indicated that in man the estrogens actually create a favorable distribution of serum cholesterol between the alpha and beta lipoprotein moieties. Work from one laboratory in particular indicated that female hormones also selectively protect the coronary vessels of birds from atherosclerosis. On the other hand, other experimental studies had shown that estrogens generally cause a hypercholesteremia and a subsequent increase in lipid deposition in the aorta of animals. The female rat, for example, is exceptionally susceptible to hypercholesteremia when fed a diet containing cholesterol and bile salts. The experience of this laboratory has shown that femaleness or estrogen treatment favors hypercholesteremia and cardiovascular lipid deposition in more than one animal species. Apparently, the sex hormone regulation of cholesteremia may depend in part on the species and on the dietary conditions imposed. Although some laboratories have reported that preliminary studies with low levels of estrogens are promising, attempts to treat men with coronary artery disease with sex hormones have not been of sufficient duration and scope to warrant definitive evaluation.

Another endocrine approach to the treatment of hypercholesteremia has been the use of thyroid hormone. It has been extensively demonstrated in experimental studies that hypothyroidism induced either by antithyroid drugs such as thiouracil or by treatment with radioiodine favors hypercholesteremia and subsequently an increased susceptibility to atheromatous lesions. Both thyroxine and potassium iodide have been used to lower the cholesterol level of experimental animals. From a clinical point of view, except in cases of hypothyroidism, the use of thyroid hormone to treat atherosclerosis is not always a desirable approach. However, more research into the thyroidal aspects of cholesterol regulation is necessary.

Recently, work from our laboratory has shown that uracil, a naturally occurring pyrimidine, also affects the thyroid and causes hypercholesteremia and increases cardiovascular lipid deposition. More recent studies into the relationship of pyrimidine metabolism and atherosclerosis have shown that orotic acid, for example, can in one experimental design counteract this uracil effect and dramatically protect the female rat against the development of atheromatous plaques. These latter studies are mentioned only to demonstrate that the thyroidal and gonadal regulation of cholesterol metabolism may not be independent phenomena.

Obviously, the answer to treating atherosclerosis cannot come until the metabolic defects favoring this disease are recognized. To the physician who is faced with the problem at hand, namely, relieving anxiety and pain, and arresting the fatal progress of disease, this may sound like an ivory-tower approach. In general, however, present experimental evidence is not very strong on the use of any one agent in protecting against atherosclerotic disease. A well-balanced diet offering all the required nutrients but not at excessive levels, a diet absent or low in certain nonessential ingredients which have been implicated in experimental hypercholesteremia, is still a good stopgap measure. There is, of course, no guarantee that dietary moderation and intelligent eating habits will spare all or even a large percentage of susceptible individuals from a coronary artery event, because both genetic

and endocrine factors may intervene.

What is the ultimate answer in the light of what is known to date? The hypothesis favored by the author is that the answer to the problem of atherosclerosis will come when the metabolic defect associated with genetic susceptibility is unraveled. The solution, of course, will be simplified if there is one common defect which manifests itself at different degrees in the majority of individuals. The defect may reside in cholesterol metabolism. On the other hand, there is a likelihood—and it is supported by some experimental evidence—that the primary insult may take place in some other metabolic pathway and that changes in cholesterol metabolism only reflect this error.

It is well recognized that the widespread interest in experimental atherosclerosis has led to valuable discoveries related to the biochemistry of the lipids. A few years ago Gofman and his colleagues adopted and refined ultracentrifuging technics for measuring the concentration of the lipoprotein moieties of serum. The circulating cholesterol is present as part of labile physicochemical lipoprotein moieties of various size and density, and Gofman's hypothesis proposes that elevation of certain of these lipoproteins may be a better diagnostic index for detecting atherosclerosis in patients. Although Gofman's hypothesis remains a controversial issue, increased interest in the circulating lipoproteins was in part stimulated by these studies. As a result newer and potentially very valuable information about the behavior and composition of lipoproteins has been made available by a number of laboratories.

In the same sense, continued interest in the metabolic pathway of cholesterol, aside from the contribution to atherosclerosis research, is bound to reveal vital knowledge about other diseases and conditions. Therefore, present interest in the role of antibiosynthesizing agents, for example, should be indeed encouraged. Obviously physiologic controls of the synthesis of cholesterol exist about which we are not aware. If certain drugs are found to be effective in controlling cholesterol metabolism, then a search for the active in vivo principles will be made easier. As a result metabolic dyscrasias, if they exist, in people who are prone to atherosclerosis may someday be corrected by drugs. Finally, as has been pointed out, perhaps the most striking impression is wide differences in susceptibility, which are not always accountable by dietary habits, among people prone to atherosclerosis. The clinician is continuously aware of such differences. The question which occurs to many of us is whether some individuals have unrecognized inborn errors of metabolism. Naïve as it may seem, this consideration can perhaps be applied to a number of diseases whose causes are still unknown. The difficulty, of course, in detecting purported inborn errors may be because only partial blocks in metabolism occur. If such errors were based on relatively more complete metabolic blocks such as in phenylketonuria, for example, the likelihood of detecting the metabolic defect would be more promising. Needless to say, there is need for intensive research on biochemical systems as related to hypercholesteremia and atherosclerosis.

From the vantage point of the experimentalist there is great promise that many of the present studies and those which will eventually evolve from these efforts will bring into sharper focus the metabolic defect or defects associated with the appearance of atheromatous lesions. There are available many legitimate leads which for the most part are based on clinical and epidemiologic observation. Therefore, aside from the excellent dietary studies, the genetic and endocrine aspects should be exploited more fully at the experimental level.

It is the responsibility of those in this field to keep the experimental evidence in proper perspective. Since the exigencies of disease cannot always afford the delays necessary in the development of the ideal treatment, the selection of available drugs is based on the accepted judgment of the experts. In a sense, all drugs to some degree are calculated risks if they alleviate the disease and pain but outweigh the side effects. At the present time, the search for agents which can prevent or delay a fatal coronary attack has not progressed beyond this point.

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Postgraduate Clinical NOTES

120. CORONARY THROMBOSIS

The coroner-physician is impressed by the frequency of coronary deaths before, during or after illicit sexual intercourse, as compared with the rarity of sudden death during marital intercourse. Acute pulmonary edema after coitus is often the only symptom in young matrons with mitral stenosis. In some of these patients, pulmonary edema occurs only when a liberal salt intake during the premenstrual period has resulted in weight gain. Ordinarily, licit intercourse and the auto-erotism of the young can be considered merely as forms of physical exercise. Similar physical activity, associated with guilt or apprehension, may precipitate much more serious results in older persons.

Although limitation of physical activity is often emphasized in the patient's instructions, it is probably not an extremely important factor in the progress of chronic disease of the heart. Sudden unaccustomed activity and the Valsalva experiment—as in exertion during defecation, for example—certainly can precipitate heart attacks, including paroxysmal tachycardia, and sudden death or onset of pain in those with chronic coronary occlusion. Nevertheless, even the hard day's work of a manual laborer may cause no symptoms until after he has been recumbent for hours. If salt intake is rigidly enforced, such a patient may remain symptom-free for months or for years. In general, those who enjoy regular physical activity have later onset of initial myocardial infarction or angina and better prognosis than patients who lead sedentary lives.

Emotional stress is an unavoidable part of life. Likewise, hereditary predisposition to heart disease cannot be altered. It is possible, however, to control one contributory factor with a diet low in salt and animal fat.

William Dock, Stress and the heart, *The Heart Bulletin*, July-August 1959, p. 73

Statistics show a continuous and striking increase in the incidence of diabetes among blind persons in the United States and England. This increase, in addition to the indeterminate number of diabetic patients with visual defects not defined as total blindness, creates an important therapeutic problem. Various devices for measuring foods and insulin, sterilizing equipment, injecting insulin, and testing the urine contribute to the self-sufficiency of the blind diabetic patient.

Management of the Blind Diabetic

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THE following seven case reports are indicative of various degrees of self-management by blind and near-blind diabetic patients. These reports also serve to prove that many blind patients are capable of utilizing the several technics which are necessary in their daily routine of living with diabetes.

MORRIS MARGOLIN

Case Reports

Case 1—The patient is a 24 year old single woman who is a home teacher of the blind. She has had diabetes since she was seven years old. Except for minimal light perception, which served no useful purpose, she had been totally blind for less than two years before she came under my observation. The blindness was due to diabetic retinopathy, and her vision had deteriorated for two years before she became completely blind. The diabetes had remained rather stable in spite of two instances of coma during and prior to adolescence and except for poor control during her teens. The usual daily requirement is 40 units of NPH insulin, and it fluctuates only slightly.

The patient graduated from college at the age of 22 years, and she obtained her degree after she had become totally blind. She has learned the technic necessary for self-maintenance by blind persons, and she had prepared herself for her position as a teacher of the blind. She came to Omaha in the summer of 1957 to assume her present position. She was accompanied by her mother, but in deference to her daughter's wish to be totally self-dependent, the mother remained only long enough to locate an apartment and to see that her daughter was settled.

Since her mother left, the patient has lived alone, has done her own household work, has cooked and prepared her food, has adminis-

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Adapted from a presentation at the Postgraduate Course in Diabetes, University of Nebraska College of Medicine.

tered the insulin herself, and has tested her urine for sugar, all without the help of persons who can see. Her work requires that she make frequent visits to the homes of her pupils in Omaha and in a large surrounding territory. This she has managed to do by the use of city and interurban buses and by walking the intervening distances using a cane.

Since it was found that the patient was dependent for her diet prescription on her memory, and since this was regarded as unsatisfactory and likely to lead to a compounding of errors, she was advised to make a Braille transcription of her diet and the booklet "Meal Planning and Exchange." She did this with her mother's help, and she now uses this Braille copy as a ready reference.

She measures her insulin by a very simple and ingenious method which she worked out with her mother's aid. This consists of using a strip of cardboard equal to the measurement of 40 units of insulin on the scale of her syringe. She fills the syringe with an excess of insulin, places the measuring strip between the top of the barrel flange and the bottom of the head of the plunger, and expels the excess of insulin into the vial until the head of the plunger and the flange of the barrel are exactly separated by the intervening strip of cardboard. Although this method was very satisfactory, it had two faults. The ends of the cardboard strips tended to soften and curl, and the method did not provide any means of varying the dose when necessary. A set of strips, therefore, was prepared by using light but strong plastic material. Each strip was made long enough to permit the administration of a definite dose. The doses that could be administered with the various strips were brailled on the strips. The difference in the doses which could be administered with the various strips was 5 units.

The patient uses a Busher automatic injector to administer the insulin, and she has found this device very satisfactory. When she tested her urine with CLINITEST® reagents, she was dependent on her associates who could see. Since such persons were not always available, she was taught how to test her urine by the Covey method.[1] Since she is not subject to ketosis, routine testing for ketonuria does not present any problem.

Case 2—A man, aged 46 years, had an advanced visual handicap due to diabetic retinopathy. He lived in a nearby community and had to make frequent visits to the outpatient clinic. On these occasions, he had to stay in Omaha for two to three days for observation. During these periods, he was deprived of his usual source of help. His vision was not impaired sufficiently to cause any difficulty in food selection or ambulation, but he was unable to read the scale on the insulin syringe. He, therefore, was instructed in the use of the Cornwall syringe.

Case 3—A man, aged 58 years, was known to have had mild diabetes for nine years. Total loss of vision due to bilateral thrombosis of the central veins of the retina had occurred a year and a half after the diabetes was discovered. There was a period in which small doses of insulin were required to control the diabetes, but he gradually has been able to discontinue the use of insulin. He has not required any insulin in the succeeding five years. During the period it was required, he used the Cornwall syringe for self-administration.

Case 4—A widow, aged 59 years, who lived in a small city in California, came under my observation while she was visiting friends in Omaha. She had a high degree of diabetic retinopathy and impairment of vision which was sufficient to prevent her from reading the scale on her insulin syringe. She, therefore, was instructed in the use of the TRU-SET®[2] attachment. When the patient was last heard from, she was getting along very well.

Case 5—A woman, aged 35 years, had had diabetes for 25 years. Cataracts had developed and had limited her visual capacity until she was unable to read the scale on her insulin syringe. She was instructed in the use of the Tru-Set attachment.

Case 6—A married woman, aged 60 years, had a severe diabetic retinopathy and vitreous hemorrhages. Her husband prepares her dose of insulin before he leaves for work very early in the morning. The patient has learned to administer the insulin herself.

Case 7—A married woman, aged 56 years,

TABLE 1

INCIDENCE OF DIABETES AMONG BLIND PERSONS*

STATE	1940 TO 1941	1949 TO 1950	1953	1954	1955	1956	1957
Average for 20 states	1.5						8.5
Massachusetts	3.8	8.0	13.9		18.0†		
New York	4.5			12.7	15.3	14.6	
California	2.0				4.0		

*The incidence is expressed in per cent.

†From July 15, 1954 to April 15, 1955.

has had diabetes for 35 years, and she has been totally blind for five years. The blindness is due to diabetic retinopathy. She requires two doses of insulin a day, and her husband assists her in measuring the doses. He prepares the morning dose, which she administers herself. He then prepares the second dose, which is placed in the refrigerator. The patient administers this dose late in the afternoon, before her husband returns from work.

Scope of the Problem

In the United States and in a few other countries, the legal definition of blindness is "a visual acuity of less than 20/200 in the better eye at maximal correction" or, with normal acuity, "a narrowing of the fields of vision subtending an angle of less than 20 degrees." This definition, which admittedly is liberal and includes defects short of total blindness, still excludes a sizable proportion of visual handicaps deserving therapeutic consideration. This is true particularly of diabetic retinopathy, which has a tendency to progress slowly and usually is associated with maximal changes in the periphery in all but the later stages of the disease. Therefore, any statistical data relative to blindness among diabetics must be evaluated with these points in mind.

Table 1 shows the incidence of diabetes among blind persons in a group of 20 states and in three individual states in the years 1940 to 1957 inclusive. The data on which this table is based were furnished by Dr. F. M. Foote[3] of the National Society for the Prevention of Blindness and by Dr. Howard F. Root.[4]

The evident disparity in the incidence of diabetes among blind persons in the different states probably reflects the varying degree of efficiency in case-finding in these states. In spite of this disparity, one important fact is plainly evident, namely, the continuous and striking increase in the incidence of diabetes among the blind in all of these states. This increase may be accounted for in part by a better reporting of cases. In the main, it must be attributed to the prolongation of life, to the complications among diabetic patients of all ages, and to the increased incidence of diabetes and blindness among our aging population. Statistical data from England show a similar increase.[3] On the whole, this reflects a trend which may continue for an indefinite period before leveling off.

It has been estimated that 334,000 persons in this country were blind in 1955.[3] More recently, Miss C. Edith Kerby[5] has made the following calculations based on sample studies and census estimates in several states. In 1940, the number of blind diabetic persons was 2.4 per 100,000 population. By 1957, this number had increased to 16.5 per 100,000. In 1957, 8 per cent of diabetics in this country were blind. Translated into actual numbers, approximately 3200 diabetics were blind in 1940, whereas this number increased to 28,000 in 1957. These figures are based on a population of 133 million in 1940 and 170 million in 1957.

The figures for the state of Massachusetts[4] are even more impressive because of the high degree of consciousness of this state in the fields of blindness and diabetes. In 1949, diabetes was present in 8 per cent of 800 new

cases of blindness; in 1953, it was present in 14 per cent of 800 new cases, and in the nine months ending April 15, 1955, it was present in 18 per cent of 700 new cases. This incidence of 18 per cent is more than double the average incidence of diabetes among blind persons in 20 states in 1957 (table 1). With the addition of the indeterminate number of diabetics with visual defects outside the limits of the legal definition of total blindness, the full significance of the problem is realized.

Educational and Informational Material

Educational and informational material is very necessary for diabetics. It can be supplied to blind diabetics by Braille transcriptions of diabetic manuals, meal planning booklets, diet prescriptions, recipe books and the *ADA Forecast*. Transcription services in Braille are available in most centers, and information regarding such services can be obtained from local or state agencies for the blind. A recent communication from the American Foundation for the Blind[6] contained the information that material from the *ADA Forecast* is being placed on phonograph records for use by blind diabetics.*

Measurement of Foods

The correct amount of foods such as meat and fruit can be estimated by feeling. Crackers and slices of bread usually are of standard size, and need only be counted. For persons who insist on more accurate measurement, a gram scale with raised markings for touch reading is available.†

Measurement of Insulin

Case 1 illustrates the high degree of ingenuity possible for blind diabetics in developing their own devices. However, such devices are not always satisfactory for elderly persons who lack the necessary skill to use them. The following syringes have been found useful for blind diabetics.

The Cornwall syringe—This is a 2 cc. syringe which originally was devised for use by technicians in obtaining exact and equal quantities of chemical solutions repetitively. There is a spring mechanism on the plunger which retracts it to a point set to obtain the desired quantity, and there is a locking device which secures the plunger at this point. The syringe is manipulated simply by inserting the needle into the insulin vial, depressing the plunger as far as it will go, and allowing it to draw up the insulin automatically. This syringe has two disadvantages: (1) It is calibrated in fractions of a cubic centimeter instead of in units; therefore, it must be set by a person capable of converting units of insulin to fractions of a cubic centimeter; and (2) the large size of the syringe, including the retracted plunger, makes it awkward to handle.

Insulin syringe with the Tru-Set attachment[2]—This recently developed attachment for the accurate and repetitive measurement of insulin consists of a metal slide bar which is attached to the plunger of a 1 cc. insulin syringe, a stop which is attached to the collar on the barrel of the syringe, and a knurled set screw on the bar which controls the stopping point of the plunger. The screw is set to provide the proper dose of insulin, and this setting can be made by any person who can see. All that the blind diabetic needs to do is to pull the plunger out until it stops, insert the needle into the insulin vial, depress the plunger to introduce air into the vial, and withdraw the insulin. An important advantage of this attachment is that it permits the separation of the plunger and barrel for cleansing and boiling without disturbing the setting. Another advantage is that the attachment can be employed with a 1 cc. insulin syringe of any make.*

Both the Cornwall syringe and the syringe with the Tru-Set attachment have the disad-

*Since this article was written, "Information for Blind Diabetics," published on four records, has been made available, and may be obtained from the regional libraries serving the blind.

†This scale may be obtained from the American Foundation for the Blind, 15 West 16th Street, New York 11, New York.

*The VIM insulin syringe with the Tru-Set attachment is marketed by the MacGregor Instrument Company of Needham, Massachusetts, and may be obtained from any surgical supply house.

vantage of being rather inflexible when multiple daily doses of different sizes are required. One answer to this disadvantage is the use of more than one syringe, each of which is set for the desired dose and marked so that the dose can be recognized by the patient. Another and more simple answer might be the proper premixing of types of insulin with a different rapidity of action in order to provide a satisfactory single daily dose for the patient.

Sterilization of Equipment

Although the syringe with the Tru-Set attachment can be taken apart for boiling, this is not possible with the Cornwall syringe. In any case, boiling may be a cumbersome procedure for some blind persons. My experience with isopropyl alcohol as a sterilizing agent for insulin syringes has been very satisfactory. I have not observed a single instance of infection in a case in which this agent was used.

The syringe with the needle attached should be filled with the alcohol to the point of stoppage, emptied and refilled several times, and then shaken several times to expel all of the alcohol before the syringe is filled with insulin. The American Foundation for the Blind has just announced a 5 cc. STERITUBE® suitable for use with an insulin syringe with the Tru-Set attachment.

Guiding the Needle Into the Insulin Vial

This problem was partially overcome by the patient in case 3, who used his finger covered with an alcohol-soaked pledget of cotton to guide the needle to the center of the rubber stopper of the insulin vial. However, he often found it difficult to avoid striking the metal parts of the cover or running the needle over the edge. A needle guide made to fit the shape of the insulin vial has been offered by the American Foundation for the Blind. This guide was obtained for the patient in case 1, but she did not find it very satisfactory. A more satisfactory guide of a funnel type is being developed in the laboratories of Eli Lilly and Company[7] and independently by the American Foundation for the Blind.[6] I have had an opportunity to try a model of each of these guides, and both of them appear to be very promising.

Injection of the Insulin

In my experience, injection of the insulin has not presented any problem for most blind diabetics. Some of these patients have found the Busher injector very helpful. However, this injector fits neither the Cornwall syringe nor the syringe with the Tru-Set attachment.

Testing the Urine

The Covey test[1] for sugar depends on a fermentation process. A pea-sized piece of fresh compressed yeast is placed in a one-half ounce homeopathic vial, and the vial is filled with urine. A thin rubber finger cot is rolled to the tip and slipped over the mouth of the vial. The finger cot may be secured with a rubber band. After the finger cot has been applied, the mixture is shaken. It then is allowed to stand for 10 to 30 minutes at room temperature. If sugar is present in the urine, fermentation will take place and cause the finger cot to bulge. The amount of bulging is a rough indication of the amount of sugar that is present in the urine. The reaction may be hastened by placing the vial close to a source of heat.

Although a test for ketonuria is very desirable in cases in which this condition has a tendency to develop, such a test is not available for blind persons. However, in cases in which there is a tendency for ketonuria to develop, the presence of large quantities of sugar should lead the patient to consult his physician or to have a sighted associate perform a test for acetone.

Aids for the Near Blind

The American Foundation for the Blind is featuring an inexpensive hand-held lens and a similar lens with a stand for use by patients with minor visual handicaps. Special glasses with a magnification to counteract the visual defect have recently been devised and can be obtained on prescription by an ophthalmologist.[8] These glasses have the following disadvantages: (1) The visual defect must have become stable, which is very unlikely in cases of

diabetes in which retinopathy is present or cataracts are developing; (2) the field of vision is strictly limited and the object to be visualized must be brought extremely close to the eye and to an exact distance from it, and (3) the glasses are likely to be expensive. I have not had any experience with these devices, but I believe that the less expensive magnifiers are worth a trial and may prove very useful in reading the scale of the insulin syringe and educational material.

Comment

Case 1 represents the ideal in total self-management by a blind diabetic. The remaining cases are examples of partial self-management. The patients in cases 2 and 3 were observed before the development of the Tru-Set attachment for an insulin syringe. Cases 4 and 5 are examples of the use of the Tru-Set attachment by blind diabetics. In cases 6 and 7, the measurements were made on a standard insulin syringe by members of the families for self-administration later by the patients.

Summary

In three of the seven cases which I have reported, the patients were totally blind; in the four remaining cases, the patients were partially blind. In one case in which the patient was totally blind (case 1), the patient lived alone and was self-sufficient in every phase of her diabetic management. In the two other cases in which the patients were totally blind, the patients were self-sufficient as far as their needs were concerned.

Statistical data reveal a uniform and steady increase in the incidence of diabetes among blind persons in this country and in England. The total number of blind persons in this country is impressive, but it does not include many persons with lesser visual handicaps who deserve therapeutic consideration. A combination of these facts clarifies the full importance of the problem.

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It is the responsibility of the physician to exercise proper wound management in the care of so-called minor wounds, and it is important to treat such wounds according to basic surgical principles. The author suggests that the most effective means of establishing tetanus prophylaxis is to immunize the general population with tetanus toxoid, a program that should be the responsibility of the entire medical profession.

A Physician's Responsibility in Caring for Emergency Patients

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THE physician's responsibility in the care and management of the emergency patient has been well established, as is evident in the many publications that have appeared on the subject.[1-4] Most reports have emphasized the management of hemorrhage and shock and the treatment of thoracic, neurologic, abdominal and orthopedic injuries. So much has been written about wound care that any new paper on this subject would seem to be superfluous. Re-emphasis of this aspect of emergency treatment is justified, however, by the attention given in civilian practice to wound suture rather than to actual care of the wound itself.

Concomitant with wound management is tetanus prophylaxis, a matter of concern in all soft-tissue injuries. In our emergency room it causes more complications than any other phase of wound management.

This report concerns these two aspects of wound care, as applied principally to the ambulatory patient. Often such a patient regards his injuries as minor; however, the physician's responsibility for proper care and management is as acute and real as if a major wound had occurred.

Early Wound Management

One should distinguish between wound care and wound suturing. The former must conform to surgical principles, whether the wound is major or minor. A certain sequence of management should be followed for every wound, with the understanding that every wound is contaminated and it is the physician's responsibility to prevent further contamination. Therefore, the following procedure should be employed for every wound, large or small:

1. All personnel concerned with the patient should use masks, caps and gloves.
2. Provide for adequate anesthesia.

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3. Cover the wound with sterile dressing, and clean the adjacent skin edges with mild soap and water. This preparation should be as efficient as if one were scrubbing the hands for an elective surgical procedure.

4. Drape the wound with sterile skin towels.

5. Irrigate the wound with copious amounts of normal saline solution.

6. Remove all devitalized tissue and foreign material and irrigate the wound again with normal saline solution.

7. Secure hemostasis.

8. Remove drapes and gloves and, with clean gloves, cover the wound again with sterile dressing and "reprep" the skin, using soap and water.

9. Redrape the wound and, with clean instruments, do the repair.

These principles may seem rather rigid to apply to all wounds, even minor lacerations; nevertheless, they are basic surgical principles of wound care. The dabbing of various antiseptic solutions in and about a wound serves little purpose, nor can any amount of antibiotics replace adequate care. These features of wound management demand our fullest attention, especially with the use of the newer methods of tetanus prophylaxis discussed later.

In most instances, primary closure may be used for a minor laceration encountered in civilian practice. A minimum amount of fine catgut, preferably 4-0 plain, is used to obliterate the subcutaneous dead space. For skin closure, 4-0 silk or nylon is preferred. A fine, dry gauze or TEFLON® dressing is employed to cover the closed wound. The use of ointmented dressings for wounds is discouraged in our institution.

Occasionally, delayed closure of a minor laceration is required, particularly in cases of injuries incurred during a disaster, such as a tornado, and of wounds simulating wartime injuries. All bite wounds except those involving the face, whether human or animal in origin, are best treated by delayed closure.[5]

Tetanus Immunization

The problems of tetanus prophylaxis in patients with minor lacerations arise primarily in those individuals who have not received adequate tetanus immunization or when the injury occurs 10 years or more after immunization.[6-8] Under such circumstances tetanus toxoid does not afford immediate protection; passive immunization with tetanus antitoxin is considered the procedure of choice.

However, tetanus antitoxin may cause complications, even when the skin test is negative. There are well-documented cases of delayed serum reaction manifested by skin reaction and peripheral nerve palsy.[9] Opinion is divided, therefore, as to the advisability of administering tetanus antitoxin. Some advocate its use in all soft-tissue wounds when past immunization against tetanus is incomplete. Others consider the nature, duration and extent of the wound as factors governing the employment of the antitoxin. The latter approach seems reasonable in the light of our present concept of tetanus infection; *Clostridium tetani* are found in soil and require devitalized tissue and anaerobic conditions for growth.

It is difficult to state positively when tetanus antitoxin should be administered. Clinical data show that puncture and penetrating wounds, most of which are considered trivial by both patient and physician, cause many of the cases of tetanus reported in civilian life.[10] The responsibility for omitting tetanus antitoxin in selected cases rests with the attending physician and his appraisal of the wound and its cause and, above all, his ability to insure adequate wound cleansing.

The dosage of tetanus antitoxin for nonimmunized patients has also been a matter of much speculation. In most casualty services 1500 units of tetanus antitoxin is considered the so-called standard dose. However, a number of authors[10-12] have emphasized the inadequacy of this dosage and have suggested a minimum of 5000 to 40,000 units for a protective and sustained serum level of antitoxin. Recent animal experiments indicate the protective serum level is variable,[13] and the protection level required for man is unknown.[8]

Considering these factors and emphasizing wound care, I believe that 1500 units of tetanus antitoxin probably affords sufficient protection in patients with comparatively clean wounds where passive immunization is re-

quired. However, if the wound is large and grossly contaminated or is seen 24 hours or more after injury, available data[10-12] suggest that a minimum of 5000 units be administered and increased as indicated.

In the management of the patient who manifests a positive skin test to tetanus antitoxin (presumably horse serum), and whose wound and immunization history demand its administration, most institutions employ a desensitization procedure using small doses of tetanus antitoxin. However, recent experimental and clinical studies[8,14] have demonstrated that such patients excrete the antitoxin so rapidly that a protective blood level is seldom obtained. Furthermore, Turner and associates[13,15] have established in animal experiments the bactericidal effect of TERRAMYCIN® or penicillin or both against the vegetative form of *Cl. tetani* organisms, with Terramycin being superior. The significance of these observations has led the Johns Hopkins Casualty Service to administer Terramycin in doses of 500 mg. every eight hours for one week to children and small adults and 2 gm. to large adults who are sensitive to horse serum, as a prophylactic procedure against tetanus.[16]

Since their results are quite convincing, we have instituted a similar regimen in our emergency room, realizing that if the antibiotic is to be employed it must be given within a few hours after the injury and, even more important, after meticulous cleansing of the wound. The method described for tetanus prophylaxis in patients with minor lacerations is simple and rests essentially on experimental data; however, when it is employed, it is the responsibility of the physician to practice even more aggressive wound care and not be lulled into a false sense of security by the protection of an antibiotic umbrella.

As an alternative, bovine tetanus antitoxin is available, and Turner[4] has also shown the feasibility of using human serum for such purposes.

One other point of importance pertaining to tetanus prophylaxis may be mentioned. It is the physician's responsibility to emphasize to the general public the importance of active immunization with tetanus toxoid. This safe and most effective immunologic procedure known against tetanus has proved its worth in military experience and deserves more attention than it has received for civilian application. Furthermore, once active immunization has been initiated, these persons should be encouraged to receive booster injections every two to four years to maintain a protective serum level of antitoxin.

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Medication of the Ear, Nose and Throat

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Potent therapeutic weapons for treating diseases of the ear, nose and throat can be used as effectively by the nonspecialist as by the specialist.

In the absence of bacteriologic investigation, treatment of external otitis must be based largely on trial and error.

Systemic administration of antibiotics or long-acting sulfonamides should be considered in obstinate cases of chronic suppurative otitis media.

Effective treatment of nasal congestion depends on knowledge of nasal physiology, histopathology and bacteriology and on observation of local and systemic side effects.

Infections of the throat caused by deep-seated bacteria should be treated systemically; locally administered antibiotic and chemotherapeutic agents may be effective in superficial infections.

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THE diagnosis and treatment of diseases of the ear, nose and throat lie within the immediate sphere of clinical activity of every physician who looks at an ear, peers into a nose, or examines a throat. These structures are by no means the exclusive domain of specialists more or less limited to a circumscribed anatomic region of the body. Here, the role of the physician-at-large can be substantial. It is he who is generally first on the diagnostic-therapeutic scene, be it the patient's home or the doctor's office, and it is his responsibility to recognize the area in which the patient's ailment lies, to know what symptoms and signs to look for, what treatment to prescribe and, equally important, when to obtain specialized knowledge. By subscribing to these pragmatic dicta, the attending physician will salvage a considerable number of patients formerly sacrificed to ineptness, indecision or ignorance. Today, potent therapeutic weapons can be used as effectively by nonspecialists as by specialists. Even when specific cures are not extant, much can be done to alleviate the discomforts of patients by paying attention to an old, yet neglected, relationship, namely, the effect of diseases of the body on the patient's mind and emotions.

External Otitis

It has been variously estimated that infection of the external auditory canal (external otitis) constitutes from 5 to 40 per cent of all

diseases of the ear seen in the United States, the wide variation being due to sectional differences in temperature and humidity. The external auditory canal is always accessible to the external world. Microorganisms are carried into the ear with the fingers or foreign bodies which are introduced for the purpose of cleansing, or they may be brought into the ear quite incidentally by air or water. Once they are lodged in the external auditory canal, they thrive in a moist chamber which normally contains ear wax and detritus which comprise a suitable culture medium for many bacteria and fungi.

To a large extent, intelligent selection of medication for external otitis depends on the bacterium or fungus that is responsible for the infectious process. External otitis may be caused by any one of a number of gram-positive or gram-negative bacteria and fungi. Among the more common causes are *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), hemolytic *Staphylococcus aureus*, *Staphylococcus albus*, diphtheroids, *Escherichia coli* (*Bacillus coli*) and the various fungi, notably *Aspergillus*, *Actinomyces* and *Monilia*. It is now believed that the etiologic role of the fungi has been overemphasized, and that external otitis is due predominantly to the gram-negative *Ps. aeruginosa*.

The most common types of external otitis include furunculosis, otomycosis, and eczematous dermatitis. *Furunculosis* occurs in the outer third of the external auditory canal, usually as the result of infection of the hair follicles and sebaceous glands by *Staph. aureus* or *Staph. albus*. It often follows trauma due to scratching or to vigorous self-attempts at removal of ear wax, or to discharge emanating from within the middle ear. A well-developed furuncle causes considerable discomfort and distress. Pain sometimes is out of all proportion to the size of the lesion.

Prompt and energetic measures should be instituted for the relief of pain. This may require the use of anodynes as well as the local application of infrared irradiation, short-wave diathermy, an electric pad or a hot water bag. For home use, insertion of a cotton wick saturated with a 5 per cent solution of aluminum acetate can be helpful. Incision of an offending furuncle is seldom advisable because of the danger of spreading infection into adjacent tissues. The most valuable single therapeutic measure in the treatment of painful furunculosis consists of administering full doses of one of the antibiotics or sulfonamides for several days. This generally accomplishes more than all other therapeutic measures combined.

Otomycosis occurs as a troublesome fungous infection of the external auditory canal. It causes itching and soreness, and it occasionally may cause pain. The canal may be filled with gray, green or black masses which resemble wet blotting paper and create a sense of fullness and a musty-smelling discharge. Otomycosis most often occurs in tropical or semitropical climates. Since at least 53 different species of fungi have been reported to be responsible for otomycosis, this disease should be considered not as a single entity but as a combination of different diseases caused by widely diverse microorganisms.

Treatment of otomycosis consists initially of gentle wiping of the external auditory canal with cotton applicators, of irrigation, and subsequent drying. In the average case of uncomplicated otomycosis, a most useful drug is a 2 per cent solution of salicylic acid in alcohol. The solution should be warmed to body temperature; then 5 to 6 drops should be instilled into the canal and allowed to remain there for about five minutes. The procedure should be repeated twice a day for several days. From time to time, the use of a 2 per cent solution of thymol in CRESATIN® (metacresol acetate) has been found satisfactory. Another method consists of packing the external auditory canal with a cotton wick saturated with Cresatin and permitting the wick to remain in the canal for 24 hours. The wick is then removed and the patient is instructed to instill 5 drops of the solution into the affected canal morning and night for several days. In the event these time-tested medicaments fail to work, some of the newer drugs to be mentioned later should be tried.

Eczematous dermatitis of the external auditory canal may occur alone, may be associated with a similar condition involving the

auricle and scalp, may have an allergic basis, or may be due to a chronic discharge from the ear. In the acute form of eczematous dermatitis, there is an initial stage of redness, itching, swelling and pain, which is followed by a stage of watery exudation and crusting. The removal of exudates or crusts produces a raw, bleeding surface. In the chronic stage of eczematous dermatitis, examination of the auricular canal may reveal only a dry scaliness or a pronounced thickening of the skin. This stage of the disease is characterized by periods of intense itching, which causes the patient to aggravate the lesion by repeated scratching.

Various types of treatment have been used for eczematous dermatitis of the external auditory canal. The treatment often has depended on whether the patient was being treated by a dermatologist or an otologist. In the acute stage, local treatment consists of cleanliness, application of a soothing ointment and prevention of scratching. Contact with soap should be avoided. In the average case, protection with a bland ointment is sufficient. If bacteriologic examination discloses *Streptococcus*, application of an ointment containing 5 per cent of ammoniated mercury will produce rapid healing. If the primary etiologic microorganism or the secondary bacterial invaders are sensitive to antibiotics or the sulfonamide drugs, a short application of ointments containing these preparations will be helpful. In the chronic stage, in which the lesion varies from a dry scaliness to pronounced thickening of the skin, an ointment containing 2 to 5 per cent of salicylic acid may be useful. An ointment containing some form of cortisone may be tried at various stages of the disease.

Until quite recently, little attention had been paid either to the pH of the skin of the external auditory canal or to the pH of solutions applied to it. Elsewhere, I have reported that these are matters that should be taken into consideration in the treatment of diseases of the external auditory canal. It is not uncommon to find that the difference in efficiency of two apparently similar drugs can be explained by the fact that one medicament produces or enhances a state of acidity, while the other produces or enhances a state of alkalinity which is unphysiologic and provides optimal soil for the propagation of infectious microorganisms. Once there are interruption of the continuity of the epithelial lining and alteration of the pH from the acid to the alkaline side, bacteria and fungi have their greatest opportunity for growth.

To some extent, obstinate external otitis must be approached therapeutically on a basis of trial and error, especially in the absence of thorough bacteriologic investigation. In private practice, bacteriologic studies are seldom undertaken routinely. In cases of obstinate external otitis, antibiotic sensitivity or susceptibility tests can aid the clinician in the selection of the most effective antimicrobic drugs for use. Unfortunately, these tests are not foolproof, and their proper interpretation requires considerable experience and judgment. In recent years, a number of solutions have been introduced for topical application in cases of external otitis. These include FURACIN® ear solution; ACHROMYCIN® ear solution; AEROSPORIN® Otic solution, which is often effective in the treatment of infections due to gram-negative microorganisms, notably *Ps. aeruginosa*; OTOBIOTIC®, which contains neomycin sulfate and sodium propionate; OTOSMOSAN®, which contains sulfathiazole and urea; and solutions, such as BIOMYDRIN® Otic solution, which contain a combination of antibiotics and derivatives of cortisone. In general, reliance on the topical application of many of these solutions should be tempered by the thought that they do not always work.

Chronic Otitis Media

Chronic infection of the middle ear, which results from acute otitis media that fails to undergo resolution, may be broadly defined as a long-standing suppuration which does not cause any signs of acute inflammation. The extent to which the original microbic invader is responsible for the tendency to chronicity is problematic, for a mixed infection invariably is present. The microorganisms that are primarily responsible for the infection include hemolytic streptococci, *Staph. aureus* and *Staph. albus*, and the secondary invaders include such microorganisms as *Ps. aeruginosa*

and *Proteus vulgaris*. The bacterial content of the discharge frequently varies from time to time, and several types of microorganisms usually are present at the same time. If one type of microorganism is eliminated by treatment, it is likely to be replaced by another type as soon as treatment is stopped. Therefore, the type of microorganism isolated from the discharge cannot be regarded as the specific cause of the disease in a particular case.

The chief symptoms and signs of chronic suppurative otitis media are a discharge from the ear, impairment of hearing, and perforation of the drum membrane. Pain is uncommon. It may be due to defective drainage, or it may be evidence of an intracranial complication. Tinnitus and vertigo occasionally are present. Impairment of hearing can be so slight as to be considered negligible, or it can be pronounced.

The discharge from the middle ear may be profuse and constant, or so scanty as to escape the patient's notice entirely. A perforation is always present in some part of the ear drum, and its location has both clinical and pathologic importance. A thin mucoid discharge with little or no odor comes mainly from the eustachian tube through a perforation in the anterior inferior quadrant of the drum. Contributing factors are nasopharyngeal and nasal infections. The discharge is either purulent or mucopurulent in cases of central perforation of the drum. Marginal and attic perforations are often associated with cholesteatoma, while a bloody discharge is suggestive of granulations or polyps.

Since a chronic discharge from the ear is a source of risk to the patient, every effort should be made to stop the discharge by conservative medical management. Operation should be performed only in selected cases. Although a discharge from the middle ear frequently will respond satisfactorily to medication, there are instances in which chronic infection of the middle ear persists despite a combination of medical and surgical procedures. A rational approach to the problem of medication requires reliance on various drugs rather than the universal application of a single form of therapy.

Water generally has a deleterious effect on a chronic discharge from the middle ear, for it reduces the resistance of tissues by keeping them moist and macerated. A chronic discharge is often reactivated when water enters the external auditory canal and seeps through the perforated drum. A patient taking a bath or shower should place a pledget of cotton into and over the external auditory canal.

A cardinal measure in the treatment of chronic suppurative otitis media is careful cleansing of the external auditory canal for the removal of pus and debris. The discharge can be removed from the canal with cotton applicators or by means of a small suction tube. Ordinarily, mass irrigation is inadvisable, for it may waterlog and macerate the skin of the canal. Continued presence of secretions in the external auditory canal almost inevitably leads to some degree of low-grade external otitis and added local discomfort. At one time, the wet treatment of chronic suppurative disease of the middle ear by means of syringing with a solution of sodium bicarbonate, boric acid or hydrogen peroxide was very popular. This, however, has lost ground to the dry method, i.e., the careful drying of the secretions with cotton applicators, followed by the use of small amounts of a nonaqueous medicament.

One of the well-known, older nonaqueous medicaments commonly prescribed for a chronic discharge from the middle ear is a mixture of 20 gr. of boric acid to 1 oz. of 70 per cent alcohol. Four or five drops of this mixture is instilled into the external auditory canal and allowed to remain for a few minutes while the patient is lying on the unaffected side. For many years, a number of powders have been used in the treatment of chronic suppurative otitis media. Among the first of these powders to be used was the one recommended by Sulzberger, that is, a powder containing 1 or 2 per cent of finely powdered iodine in boric acid. After the discharge has been cleansed from the canal, the powder is insufflated. The procedure is repeated either once a day or twice a week, depending on the amount of discharge that is present, until the ear remains dry.

The new bactericidal solutions that were mentioned in the treatment of external otitis may be useful in the treatment of chronic suppurative otitis media. Although the clinical response to the local application of these solutions has been encouraging, the number of cases in which they have been ineffective is sufficient to cause the physician to seek other medical approaches.

In cases of obstinate chronic suppurative otitis media, it is always worthwhile to consider the systemic administration of antibiotics or the new long-acting sulfonamides such as KYNEX® and MIDICEL®. Full doses of these drugs should be administered for at least a week. Surprisingly favorable results are obtained from time to time, to the delight of the patient, who has almost given up hope, and to satisfaction of the doctor, who is most pleasantly surprised. Although bacteriologic studies of the ear secretions and antibiotic and sulfonamide sensitivity tests can throw light on the choice of appropriate medication, the tests by themselves are no guarantee of a successful drying of a chronic discharge from the middle ear. The drying of the canal itself holds the secret of success or failure.

Treatment of the Stuffy Nose

The use of nasal medication is both widespread and popular. Mounting attention to nasal physiology, histopathology and bacteriology has induced many physicians to use nasal medication in a sound, rational manner, which is desirable. In an era that is still characterized by the undisciplined use of antibiotics, there is greater need than ever for intelligent therapeutics.

Physicians who use and prescribe the intranasal administration of medicaments frequently assume that the nasal mucous membrane always should react in a constant and predictable manner to the application of these medicaments. They are unaware that the environment of the nasal mucous membrane is far from constant and that it is continuously subject to change. The response to the same dose of these medicaments may vary in different cases and even in the same case. Indeed, it is axiomatic that no two noses are alike.

Intranasal medication has definite indications and purposes. If these are recognized, if the underlying pathologic condition of the nose is properly evaluated, and if the medication is employed judiciously, the clinical response frequently will be satisfactory. Nasal vasoconstrictors, for example, are among the more important drugs available for use in the nasal cavity. They relieve nasal congestion for varying periods of time, promote comfort, improve nasal ventilation, and, when rationally used, aid in promoting adequate drainage from the paranasal sinuses by opening obstructed ostia. Although these drugs afford only symptomatic relief, even temporary relief from the discomfort of nasal obstruction due to the common cold, sinusitis or nasal allergy is welcome to distraught patients. Today, a number of sympathomimetic amines have come to assume a legitimate place in the therapeutic armamentarium.

The problem of producing new sympathomimetic amines is of great importance and has been slowly gathering attention in the pharmaceutical world. Various nasal vasoconstrictors in combination with various sulfonamides, antibiotics, antihistamines, and, more recently, steroid hormones have been introduced. Some of the available combinations include such antibiotics as polymyxin B sulfate, gramicidin, and neomycin. Although some solutions containing a combination of medicaments for intranasal administration have their ardent supporters, other investigators view these nasal solutions with restraint.

In order to use nasal medication effectively and intelligently in clinical practice, it is necessary to relate the widely prescribed medicaments to various aspects of the nasal environment. Nasal medicaments should be regarded not only in terms of their inherent pharmacologic properties, but also in terms of their local effect on the mucous membrane of the nose and paranasal sinuses, on the ciliary motility, on the nasal pH, and on their systemic effect on the body itself. Effective nasal medication should not only do what the prescribing physician hopes to accomplish in the patient's nasal cavity without causing injury to the mucous membranes, but it should also not

cause harm elsewhere in the body. In general, it is highly advisable to determine the pharmacologic and the histologic effects of nasal medicaments on the nasal mucosa of experimental laboratory animals before advocating their use in human beings.

Some years ago I found that nasal vasoconstrictors with an unusually high alkaline pH may disturb the normal, slightly acid pH level present in clinically normal nasal passages, enhance irritation of the nasal mucosa, and postpone the return of the nasal mucosa from a pathologic alkaline status to a normal, slightly acid status. During an attack of acute rhinitis, acute sinusitis, or the more active stages of allergic rhinitis, the use of a nasal vasoconstrictor that lowers the abnormal alkaline nasal pH found in cases of these entities to a normal, slightly acid pH between 5.5 and 6.5 in adults, or between 5.0 and 6.7 in infants and children, in short, a true physiologic nasal pH, is most desirable for efficacious therapy.

To summarize, better local therapy depends on knowledge of the effect of nasal preparations on the nasal and sinus mucosa, ciliary motility and the pH of nasal secretions, and on observation of the presence or absence of local and systemic side effects. A nontoxic, nonsensitizing nasal medicament that is compatible with ciliary motility, that does not vary greatly in its pH from that of normal nasal secretions (pH 5.5 to 6.5), and that is nontraumatizing to the mucous membranes is most desirable in the treatment of the nasal cavity and its diseases. These attributes are most useful in clinical practice precisely because they rely on trustworthy principles underlying sound, physiologic nasal medication.

The increasing use of orally administered sympathomimetic amines for the relief of nasal congestion constitutes a revival of an old concept. Support for the efficacy of oral nasal decongestion as a therapeutic procedure is derived from various sources. As in the case of the topical use of nasal vasoconstrictors, the oral administration of nasal decongestants can be useful in the treatment of acute and subacute rhinitis and sinusitis, nasal congestion, vasomotor rhinitis, allergic rhinitis and postnasal dripping—in fact, in the treatment of all conditions in which nasal decongestion is desirable. One advantage of the topical application of nasal vasoconstrictors is that decongestion occurs rapidly, whereas 15 to 30 minutes is required for decongestion to occur after these vasoconstrictors have been administered orally. On the other hand, oral administration of decongestants will shrink all of the tissues of the nose and paranasal sinuses whereas topical application of these drugs will shrink only part of these tissues.

Oral administration of sympathomimetic amines as TRIAMINIC® has been found effective in the treatment of common diseases of the nose and paranasal sinuses. Thus far, experience suggests that oral administration of nasal decongestants will assume a place alongside the topical administration of these drugs as an efficacious procedure for the relief of the stuffy nose. Oral administration of nasal decongestants can be used either as an adjuvant to the topical application of these drugs or in place of the topical application.

Diseases of the Throat

Diseases of the throat, especially acute and chronic pharyngitis and acute tonsillitis, form a considerable part of the infections of the upper part of the respiratory tract that are treated by physicians. Acute pharyngitis, which involves the posterior wall of the pharynx, often begins with a sensation of dryness or scratchiness of the throat, which sometimes amounts to actual pain. It also may be associated with slight fever, malaise and headache. As the exudate accumulates on the reddened wall of the pharynx, hawking and rasping of the secretion occur, and a dry cough frequently develops. Cervical adenopathy, referral of pain to the ear, and cervical tenderness occur in cases in which the disease is severe.

Although the use of antibiotics and sulfonamides has altered certain aspects of the treatment of acute pharyngitis, mild types of this disease frequently will respond well to time-tried methods of treatment such as rest in bed, irrigation of the throat with hot, isotonic solution of sodium chloride, administration of 5 or 10 gr. of aspirin for the relief of pain, and

an adequate fluid intake. An effective procedure, which adds materially to the comfort of the patient, consists of irrigating the throat with 1 or 2 qt. of fluid from a container placed about 2 ft. above the patient's head. The glass or rubber irrigating tip is held by the patient, and the fluid is directed against the posterior wall of the pharynx. A syringe or douche also may be employed for irrigating the throat.

During the past few years much doubt has been cast on the value of gargles in the treatment of acute pharyngitis and acute tonsillitis. Although gargles are popular with the laity, their use has no therapeutic foundation, since the very process of gargling necessitates approximation of the posterior part of the tongue to the soft palate in order to prevent fluids from running into the larynx. Experiments with methylene blue, which were designed to demonstrate the efficiency of gargling, have demonstrated that the dye cannot be seen beyond the third molar tooth and cannot reach the tonsillar areas. Likewise, painting the throat with antiseptic solutions during acute infections is known to have only psychic value.

In cases of superficial infections of the throat, local administration of antibiotic and chemotherapeutic agents may be effective; however, their value diminishes if the microorganisms have penetrated deeply into the tissues of the throat. Actually, when microorganisms have established themselves below the surface and an abscess has formed, locally applied medicaments have little value. In cases of acute streptococcic tonsillitis, for example, all of the offending microorganisms are not found on the surface of the tonsils; actually, many of them lie deep in the tonsillar tissue. Under such circumstances, the value of lozenges, troches, pastilles, and medicated chewing gum is dubious. Deep-seated bacteria are best treated systemically; it is dangerous to rely on local medication alone in the treatment of severe infections of the throat.

Mention should be made of some of the older forms of local treatment, especially of subacute and chronic pharyngitis. Local treatment consists of removal of secretion and the topical application of a mixture of iodine and glycerin with a swab. This preparation is mildly effective, but unless it penetrates the mucosa, it is soon washed away. In cases of hypertrophic pharyngitis, treatment requires the removal or amelioration of all possible contributing causes such as infections of the nose and paranasal sinuses and irritation produced by the excessive use of tobacco. The application of a 5 to 10 per cent solution of silver nitrate directly to the areas of lymphoid hypertrophy on the posterior wall of the pharynx once a day for two or three days occasionally is helpful.

Atrophic pharyngitis (pharyngitis sicca) often is associated with atrophic rhinitis. In cases in which the disease is mild, the pharynx has a lusterless, glazed appearance. In cases in which the disease is advanced, marked atrophy of the mucosa occurs and crusts are present. Patients with atrophic pharyngitis have a feeling of considerable dryness in the throat. In order to dislodge the secretion adherent to the posterior wall of the pharynx, they often attempt to clear the throat by hawking, retching or vomiting. As a result, a chronic sore throat is not unusual.

Since it is impossible to effect regeneration of the atrophied pharyngeal mucosa at present, treatment is directed toward alleviation of the symptoms. Mandl's solution or a mixture of one part of tincture of iodine to seven parts of glycerin is applied to the wall of the pharynx. The effect of these preparations is to stimulate secretion. At the same time, 10 drops of a saturated solution of potassium iodide may be administered three times a day at meal time. The inspiration of warm, moistened air from a kettle, vaporizer or basin helps to moisten inspissated secretion.

Laryngitis

As a result of its anatomic position, the larynx is subject to a fairly large number of inflammatory processes. A husky voice is a symptom, not a disease. It is a most important symptom because it may be an early warning of serious disease in the larynx and elsewhere. Acute laryngitis occurs either as an isolated disease or as a complication of a general infection of the upper part of the respiratory

tract. In addition to its periodic occurrence during the course of influenza, whooping cough, bronchopneumonia and measles, laryngitis is also caused by vocal abuse, inhalation of irritants, dusts and gases, the drinking of extremely hot liquids, and by trauma.

Any disease or disorder that interferes with the approximation, tension or vibration of the vocal cords will cause hoarseness. This interference may be due to a number of conditions, namely, benign tumors (papillomas, fibromas, polyps and vocal nodules), malignant tumors (squamous cell carcinoma), swellings, and secretions that interfere with the approximation of the vocal cords, as well as vocal cord paralysis. Needless to say, it is impossible to make a diagnosis of laryngeal disease on the basis of a history alone. Visualization of the vocal cords by using a laryngeal mirror may in some cases mean the differentiation between a husky voice that has a cheerful prognosis and a husky voice that spells serious import if neglected.

The common attack of acute laryngitis usually lasts four or five days, but under unfavorable conditions there is a tendency for the condition to relapse and to become chronic. Unless fever is present, rest in bed is optional for the patient. If fever occurs and the general symptoms become severe, the patient should then be made comfortable in a warm, moist, well-ventilated room in which the air is moistened either by a number of water pans placed on steam radiators, by large steam vaporizers, or by steam permitted to enter the room as it leaves a running hot shower in an adjoining bathroom. Periodic inhalation of water steam gives a feeling of comfort and relief to most patients. Inhalation of steam impregnated with various aromatic substances, tincture of benzoin, menthol, oil of pine, or oil of eucalyptus, adds little to therapeutic efficacy other than a pleasant aroma.

No form of gargle has the slightest beneficial effect, since fluids taken into the mouth cannot reach the larynx. Direct topical application to the vocal cords of solutions of silver nitrate on the end of a curved applicator, once a popular procedure, is to be condemned. The ideal treatment, namely, complete vocal rest, is a difficult one to achieve except in the case of unusually cooperative patients. Inhalation of a medicament divided into very small droplets created by an aerosol nebulizer is a convenient way of treating the larynx, although in severe laryngitis the administration of antibiotics and sulfonamides is indicated.

Repeated attacks of acute laryngitis frequently result in chronic inflammation of the laryngeal mucosa. However, chronic laryngitis may come on gradually, and in such instances the most common causes are faulty or excessive use of the voice, abuse of alcohol and tobacco, nasopharyngeal infection, and the inhalation of dusty air or irritating fumes. Treatment should consist primarily of the avoidance of these factors known to produce a husky voice.

If the cough associated with a husky voice is distressing, sedatives should be prescribed together with an appropriate cough preparation. Not too many years ago, an older generation of physicians treated a cough effectively with a favorite cough mixture, an admonishment to the patient to go to bed in a moist, moderately warm room, and occasionally the twinkling hint to indulge in a reasonable dose of an alcoholic beverage. Today, younger physicians will be surprised to learn how effective such simple measures can be in the treatment of simple coughs associated with a husky voice. This is not to imply that the antibiotics and sulfonamides do not have a proper and rightful place in treatment of more serious and annoying infections of the upper and lower parts of the respiratory tract. For most simple coughs, however, a therapeutic rifle will suffice rather than a medicated hydrogen bomb.

Cross-eye does not always involve an impairment of the eye muscle. The synergism between the higher brain centers controlling convergence and divergence also may be a causative factor. Operation is frequently the most dependable remedy, but surgical results cannot be accurately predicted. The value of nonsurgical procedures should not be overlooked.

The Correction of Cross-eye

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THE goal in the treatment of cross-eye is not merely to straighten the eyes but also to make them see in unison and to behave like normally balanced eyes. One must often be satisfied, however, with a less than perfect result. Surgery alone may not always prove successful, for reasons that can be better understood when such eyes are compared with normally paired eyes, which are characterized by the following:

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1. Passable sight without glasses or with corrective glasses.
2. Straightness in distant as well as close vision.
3. Balanced movements of both eyes when looking in any direction.
4. The ability to converge with ease when a light is brought nearer and nearer to the eyes.
5. The ability to fuse images readily due to the coordination of both maculae, and the ability to maintain this fusion even when the eyes are subjected to artificial strain, as when they are made to look through prisms of specified strengths and in known positions.

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The immediate and often primary aim in treating cross-eye is obviously to straighten the eyes. Operation is frequently the most dependable remedy, especially in cases of strabismus of the convergent, or turning-in, type. When the eye turns out (divergent strabismus), eye training must be considered as a possible alternative to surgery, depending on the individual case. Least amenable to operation is strabismus of the vertical type, in which the eye turns up or down. In cases involving unsuccessful or imperfect surgical results, an occasional need for reoperation, and anxiety on the part of the patient or his family, the ophthalmologist is obligated to consider and to recommend nonsurgical measures also.

Diagnosis

Normally straight eyes may appear deceptively crossed. Epicanthus often produces a false appearance of convergent strabismus. Other congenital anomalies or acquired deformities of the eyelid may cause straight eyes to appear to be turning in, out or down. The relative straightness of the eyes can be determined by carefully noting the positions of the light reflections or "reflexes" in relation to the centers of the pupils while the patient looks at a flashlight held by the examiner just beneath his dominant eye. In normally straight eyes these light reflexes theoretically should be centered on both pupils. Because anomalous

variations may occur normally, the physician must familiarize himself with the possible normal positions of the light reflections. A broad face with wide separation between the eyes may falsely suggest a divergent strabismus. Patients who have straight eyes with severe myopia often appear to have convergent strabismus, because the normal positions of their pupillary light reflections are displaced anomalously somewhat temporally to the centers of the pupils.

In true convergent strabismus the light reflection in the turned-in eye is displaced temporally on the pupil or cornea from the normal seeing position, whereas in divergent strabismus the reflection is displaced nasally.

Cross-eye is often misdiagnosed as normal, simply because the light reflections happen to be centered on both pupils. Careful observation enables the examiner to distinguish between eyes that appear falsely crossed and eyes that appear falsely straight.

Etiology

A structurally normal eye may fail to see because of failure to develop sight soon after birth. With such discordance in sight between two eyes, binocular vision becomes rudimentary, and the "lazy" eye often, though not always, moves into a lagging, deviant position. The patient is then said to have cross-eye as a result of visual imbalance and lack of fusion and not primarily as a result of a disorder of the ocular muscles. Persistent deviation of the eye upsets the synergistic balance between the opposing muscles of the eye, producing: (1) an essentially spastic or hypertrophic muscle that must be weakened in order to restore straightness of the eye; or (2) a stretched muscle that requires shortening to attain the same effect.

This spasm in one muscle or stretching and atony in the opposing muscle which characterizes cross-eye may be due to an extraneous disorder. In the case of chronic and permanent cross-eye, the extraneous causes may be impossible to identify unless the disturbance has been followed from the beginning. We know, for example, that paralysis of a cranial nerve can lead to acute strabismus, which may clear up completely or may in turn produce a chronic strabismus essentially similar to the nonparalytic type. Furthermore, refractive disorders, such as hyperopia (farsightedness), can lead to cross-eye in some children, particularly if their vision is not corrected by eyeglasses. Left untreated, this type of cross-eye shows the same characteristics as do other types. The synergism between the higher brain centers controlling convergence and divergence also helps determine whether the eyes will be straight or crossed. Excessive activity in the divergence center leads to a peculiar type of divergent strabismus which often persists despite operation on the muscles of the eye. Training may therefore have to be directed to this divergence center to attain a reasonable balance.

Surgical Treatment

Before deciding to operate one must establish whether the affected eye is structurally normal or whether it has been damaged by cataract or corneal scar. When sight is poor, one must determine whether or not it can be improved or corrected by eyeglasses.

While judgment and proper selection of cases for operation are necessary, one cannot predict with any accuracy how straight the eyes will be following surgery, especially if the operation is performed under general anesthesia. Nevertheless, one is often pleasantly surprised to observe that a marked cross-eye has been corrected after operation was done on only one eye and one eye muscle. If necessary, the physician can perform a second surgical procedure without the risk of excessive intervention. If the operative results are poor, the eyes may turn in opposite directions; also, a false nystagmus may result from failure of the eye muscles to become properly attached to the eyeballs or from the occurrence of postoperative psychologic shock.

Following operation on an eye muscle, cosmetic improvement may be so great that the surgeon will dismiss his patient as "cured" merely on the basis of appearance, without investigating the latent ability of the eyes to see as straight eyes do. Even with so-called perfect operative results, there are often re-

sidual signs of cross-eye or imperfect binocular vision, which can sometimes be rectified by intensive postoperative training. In these cases the eyes must be amenable to training and must have passable vision. Failure to attain binocular visual coordination is said to account for persistent cross-eye following surgery. Paradoxically, even when a cross-eye is practically blind and fusion training is ruled out, satisfactory and permanent straightening may still be produced by surgery.

Nonsurgical Measures

It is a mistake to assume that cross-eye always involves an impairment of the eye muscle and that it must be treated surgically. Even current texts on eye surgery teach that, like pulleys, the eyes can be straightened fairly accurately by shortening or lengthening eye muscles a specified amount, depending on the degree of strabismus. This overlooks the fact that even after an apparently successful operation on an eye muscle, the selective movements and positions of the eyes are governed by peripheral cranial nerves and by the appropriate brain centers. Thus, straightening of the eyes may last for only a short time after the operation. Clearly, one cannot treat cross-eye solely as an organic problem. Re-education through binocular training may be necessary, much as a left-handed person requires training to use his right hand successfully.

Nonsurgical measures must be considered carefully either as supplements to or as substitutes for surgical intervention in straightening the eyes or improving sight. Eyeglasses, atropine or pilocarpine eye drops and controlled eye exercises all are useful.

The primary aim of orthoptics, or eye muscle training, is to awaken the eyes to become alive to each other. In actual cross-eye this relationship is dormant or suppressed. Training *without* surgery is often sufficient in milder cases of divergent strabismus, where operation would be valueless because of the excessive innervation emanating from the divergence center of the brain. (In more pronounced cases of divergent strabismus, operation is often advisable to reduce the strabismus and render the eyes amenable to later training.) Training can be used *following* surgery when the eyes do not spontaneously and gradually generate binocular vision.

The patient may be assigned to a trained assistant or orthoptist provided the ophthalmologist keeps close watch on the child's progress. In other cases, the ophthalmologist may train the mother to carry out his instructions. The orthoptist often employs some form of stereoscope in eye training, and although the eyes can often be made to see "straight" through such instruments, they may not remain straight otherwise. Therefore, the ophthalmologist should be sufficiently well versed in these procedures to guide his orthoptic assistant and not permit the assistant to manage the patient without supervision.

If binocular training is sufficiently intensive, the probability of its succeeding should be discernible within a few weeks. Unfortunately, children have too often been made to attend eye clinics for many months with results that make one wonder whether these "training" sessions were really advisable. In some cases eye training may be prescribed for only a few sessions in order to introduce the patient to the experience of binocular vision or to inspire visual confidence when he himself is not entirely satisfied with an objectively successful surgical result.

Conclusions

1. Cross-eye is not necessarily or primarily a problem of the eye muscles, since the higher brain centers governing convergence and divergence are important in its causation.

2. Eyes that are straight may appear crossed and, conversely, eyes that are crossed may look deceptively straight.

3. Although surgical treatment alone may straighten the eyes, the value of nonsurgical measures should not be overlooked.

4. The results of surgery of the eye muscle cannot be predicted with any accuracy.

5. Careful trial will determine which types of cross-eye can benefit from the use of drops or eyeglasses.

6. In selected cases, binocular training can be helpful if it is carried out intensively and is supervised by an ophthalmologist.

Difficult labor occurs in about 6 per cent of obstetric cases. Dystocia should be recognized within a few hours after the cervix has begun to dilate. Stimulation or sedation is instituted according to the pattern of labor, the fetopelvic relationship, and the presence of abnormalities of the presenting part. Conservatism and patience must be exercised in the use of forceps.

Difficult Labor

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DIFFICULT labor can be one of the most frustrating, enervating and worrisome experiences in the practice of medicine. Although no labor may be considered easy, the term difficult labor usually connotes a prolonged, ineffectual and exhausting labor which is ultimately deleterious to the fetus or to the mother, or to both. It occurs in about 6 per cent of obstetric cases, and it always causes anxiety. The conception and management of this complication have changed in the past 15 years, especially since cesarean section has become much safer and indications for it have been broadened. At present, we seldom see the four or five day labors which were observed several years ago, and, with the modern methods now available, a labor of more than 24 hours soon will be obsolete.

Difficult labor may be considered from three important aspects, namely, anticipation, recognition and management.

Anticipation

The forces of labor are for the most part unpredictable, but there are certain ways in which one can help the patient, and considerable information which may be gained during the prenatal period may be of much value when labor begins. The patient may be prepared for labor by an adequate diet, particularly one that contains an adequate amount of iron, calcium and protein; by exercises in relaxing; by maintaining mental complacency through reassurance; and by inspiring confidence. Nothing is more efficacious in relieving a patient's tension at the onset of labor than for her to see her obstetrician and to know that he is at hand. To have someone with her constantly during her labor also is a great boon and comfort.

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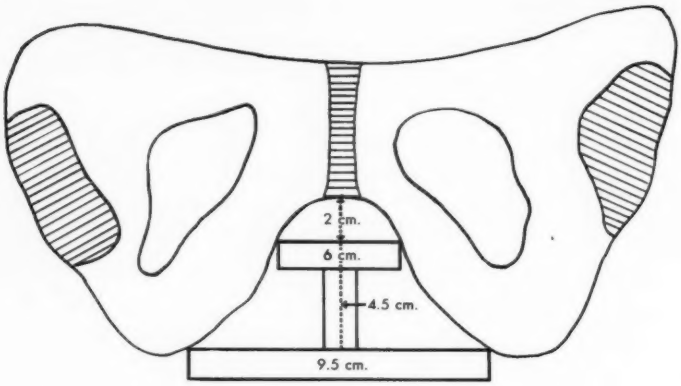

FIGURE 1. Application of pattern representing the fetal head under the subpubic arch. The upper surface should be within 2 cm. of the symphysis.

The accoucheur may prepare himself by attention to the past obstetric history, by noting the patient's constitutional type, and by careful appraisal of the size and contour of the pelvis and the size of the fetus. Inertia may be expected if the history reveals that this has occurred at any delivery except the initial one. Anatomic configuration of the parturient may suggest what to expect in labor. If she is of the typical gynecoid type, a normal delivery usually can be expected, but the more she approximates the male or android type, the more difficult the labor may be. An altered quality of uterine contractions is seen particularly in women of the dystrophia-dystocia type; that is, short and obese women who have a thick neck, hips and legs, and stubby, spadelike hands. Such women are likely to have a hypertonic uterus. The pain of the uterine contractions is likely to be disproportionate to their intensity, and the tone of the myometrium may be increased between contractions. The cervix dilates poorly, and labor is markedly prolonged.

It must be remembered that cephalopelvic disproportion and maladjustments of the presenting part, even of a minor degree, are the most frequent causes of inefficient labor. Estimation of the size of the pelvis and fetus involves careful clinical palpation and mensuration, and roentgenographic pelvimetry should be used if necessary. The parts of the pelvis most productive of information by clinical study are the subpubic arch and the pelvic outlet. A cardboard pattern of the important diameters of the fetal head offered for delivery (figure 1) will readily show the adequacy of the subpubic arch and the pelvic outlet. If the pattern fits well under the symphysis and between the ischial tuberosities, there will invariably be no difficulty from the midpelvic plane through the outlet. The distance from the point on the inferior rami of the pubis where the superior surface of the pattern impinges to the sacrococcygeal joint (best determined with the examining fingers in the vagina) must measure 9.5 cm. or bony dystocia is present (figure 2).

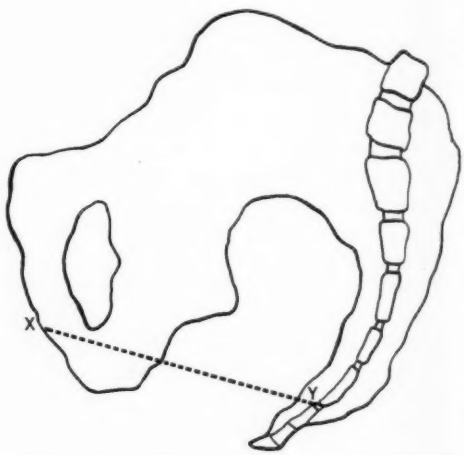

FIGURE 2. XY, pubosacrococcygeal diameter, from point where the upper surface of the pattern fits into the subpubic arch to the sacrococcygeal junction. This diameter should measure at least 9.5 cm.

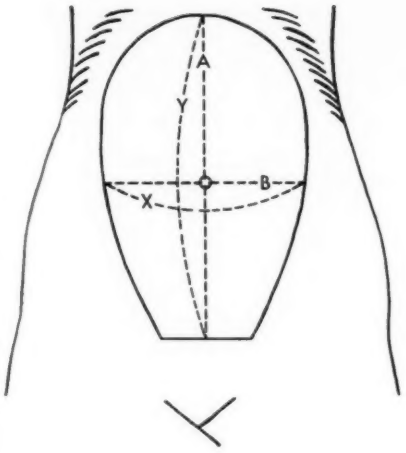

FIGURE 3. Diameters measured to estimate the size of the uterus. A, vertical length from upper border of symphysis to top of fundus taken with caliper pelvimeter; B, transverse diameter level with umbilicus, taken with caliper pelvimeter; Y, vertical length taken with tape measure over convexity of uterus; X, transverse diameter taken with tape measure over convexity of uterus.

Roentgenographic pelvimetry should be used in cases in which the fetal head is unengaged at the onset of labor, in all cases of breech presentation unless the history or physical examination indicates that the pelvis is large, in cases in which the subpubic arch and pelvic outlet are narrow, and in cases in which a previous delivery has been difficult. Although accurate determination of the size of the fetus in utero is impossible, measurements made at weekly intervals during the last four weeks of pregnancy according to the technic illustrated in figure 3 will be of considerable value in the recognition of abnormalities in the size of the uterus. If the vertical and horizontal diameters of the uterus measured with a pelvimeter and the same diameters measured over the convexity of the uterus with a tape measure exceed 105 cm. at term, the presence of multiple pregnancy, hydramnios or an overly large baby must be suspected.[1]

Weekly vaginal examinations, beginning four weeks before the expected date of confinement, will provide valuable information about the effacement and dilatation of the cervix, which should be progressive and result in the ripeness which is the prerequisite for an effectual short type of labor. A well-prepared cervix usually indicates an efficiently acting myometrium well primed with actomyosin and adenosine triphosphate provided by the elaboration of an adequate amount of steroid hormone.

Recognition

Dystocia should be recognized within a few hours after the cervix has begun to dilate. By that time, the pattern of labor which will prevail more or less throughout the first stage will have been established. Abnormalities must be recognized early. The patient should not be allowed to experience a prolonged frustrating type of labor for many hours without an attempt being made by the physician to provide supportive treatment or to alter the pattern of the labor. It is not good obstetric practice to wait 24 to 36 hours before investigating a poorly functioning incoordinate uterus which is trying unsuccessfully to expel its contents. From the time the cervix begins to dilate, labor should not last more than 12 hours with ruptured membranes or 18 hours with unruptured membranes. An accurate record of the contractions, including their intensity and duration, and the interval between them, must be kept. This record preferably should be kept by one experienced person in order to avoid errors that might result if the record were kept by different persons.

Rectal examinations should not be made too frequently, and they are best made by the same person. If the progress of labor is unsatisfactory at the end of six hours after the cervix has begun to dilate, appraisal of the situation should be made including a review of labor forces and a vaginal examination under sterile condiitons. A lateral roentgenogram of the pelvis may be most informative.

After cephalopelvic disproportion has been eliminated as a possible cause of the dystocia, attention must be directed to an abnormal position of the presenting part, and to incomplete effacement and poor dilatability of the cervix. The last two conditions usually are secondary to inefficiency of the uterine

contractions. With the data obtained in this manner, one can estimate the probable duration of labor and decide on the type of management to be used.

In appraising the efficiency of the myometrium, it is necessary to distinguish false labor, preliminary labor, primary inertia, secondary inertia, delayed labor, an incoordinate uterus, and cervical dystocia. As Reynolds[2] has shown convincingly, in cases in which the pattern of labor is most efficient the contractions are most intense at the fundus, they are less intense at the midzone, and practically no contractions occur in the lower segment. The contractions also must be regular in rate and rhythm, and of good quality and coordination. One must stand by the parturient during several contractions, time them, and test their intensity by compressing the uterine wall at various levels with the finger tip in order to obtain a true picture of the uterine action.

False labor contractions are irregular in rate, rhythm and intensity. They possibly cause some effacement of the cervix, but they do not cause any dilatation. Preliminary labor resembles false labor, but it progresses to actual labor. It is concerned with the latent period usually seen in a primigravida from the onset of labor pains until the cervix is dilated to a diameter of about 2 cm. It may last for several hours, and many cesarean sections are performed because this type of labor is not distinguished from active labor.

In cases of primary inertia, the contractions are weak and inefficient from the start, and dilatation of the cervix occurs very slowly. Secondary inertia occurs late in a labor which has been strong and effective but has caused fatigue of the uterus with resultant lack of progress. If the presenting part is engaged, the inertia is suggestive of disproportion at the midpelvis or pelvic outlet, or it possibly may be suggestive of an abnormal presentation, which should be investigated.

Delayed labor is caused by the injudicious use of analgesics and the consequent retardation of an efficiently begun labor. Incoordinate labor is characterized by strong painful contractions which fail to cause progressive dilatation of the cervix and descent of the presenting part because the pattern of the contractions is abnormal. There is a lack of fundal dominance, and coordination is absent in the various zones during contraction. This type of labor occurs most frequently in very apprehensive patients who are poorly prepared mentally for labor. It also is a common cause of constriction ring dystocia as a result of midzonal predominance.

Cervical dystocia is usually secondary to uterine inefficiency, but there may be a conglutination of the cervix, which may be primary or may be the result of scarring from a previous injury or operation.

Management

The pattern of labor, the fetopelvic relationship, and the presence of abnormalities of the presenting part must be determined early, and stimulation or sedation must be instituted as indicated. False labor may be stopped by the use of a mild sedative, such as one of the barbiturates, or by the administration of morphine if necessary. Preliminary labor is best managed by assuring the patient that she is not in active labor, by keeping her off the delivery floor, and by allowing her to walk around and to have visitors, if possible. If the preliminary labor is unduly prolonged, administration of morphine occasionally is indicated.

Primary inertia may be corrected by rupturing the membranes or by the intravenous administration of PITOCIN® if there is no contraindication. Both of these therapeutic measures may be used. Secondary inertia is treated by rest, administration of fluids, and the avoidance of stimulation that may aggravate the exhaustion of the myometrium. One should determine whether the inertia is due to disproportion at the midpelvis and the pelvic outlet. After four hours of rest, provided if necessary by the administration of morphine, labor may be started again by the intravenous administration of Pitocin if there is no disproportion.

In cases of incoordinate uterus, a sedative, preferably morphine, should be administered, with the expectation that the uterus will later

develop a better pattern of labor by itself or as a result of the intravenous administration of Pitocin. Labor delayed by analgesics may be stimulated by the intravenous administration of Pitocin while the patient is still enjoying the effects of the sedation.

Intravenous administration of Pitocin—Stimulation of labor by the intravenous administration of Pitocin is one of the greatest advances in obstetrics that has been made in several years. It makes the rhythm more regular, the contractions stronger, and the pattern more like that of a normal labor.[3] However, its use is fraught with danger, and it should be used by an experienced person.

It is best administered in a 5 per cent aqueous solution of dextrose by means of the two-bottle technic. The dilution of Pitocin in the dextrose solution should never be less than 1:1500. When the infusion is started, the number of drops of solution administered should not exceed the number required to supply one-fourth minim of Pitocin per hour. No more than 1 minim of Pitocin should be administered per hour at any time. The infusion must be stopped immediately if uterine tetany becomes evident. The administration should be continued during the third and fourth stages of labor. The drug never should be used if there is cephalopelvic disproportion or an overdistended uterus, or in cases of parity of five or more. Its use also is contraindicated in cases in which a cesarean section has been performed previously and in cases in which there is a uterine scar. It acts poorly and may be dangerous in cases of uterine infection. If fetal distress is present, the intravenous administration of Pitocin may further compromise the supply of oxygen to the fetus.

Forces delivery—When forces delivery is used, careful attention must be paid to the trauma which probably will result to the fetus, the mother, or both. The force required to deliver the fetus remains a matter of controversy. In 1867, Joulin[4] said that the combined efforts of the uterus and the abdominal muscles in expelling the fetus amounted to about 110 lb., while Duncan[5] in 1868 claimed that a pressure of only 80 lb. was necessary.

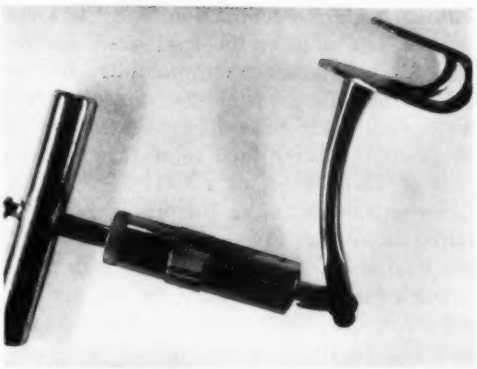

FIGURE 4. The Wylie tractionometer. As traction is applied, a movable ring moves upward on a scale and indicates the force used.

Haughton[6] averred that the uterus could contribute 54 lb. of pressure and the abdominal muscles 423 lb. Thus, the combined forces would amount to 477 lb., which would leave a surplus of 397 lb. if Duncan's figures were to be accepted. Duncan[5] thereupon challenged Haughton's estimates and argued most eloquently: "The possession and use of such power would render the forceps and cephalotribe weak and useless instruments; the mother would grind the baby as in a mortar and squeeze it through a pelvis, which under other circumstances would necessitate cesarean section. Such a power, if appropriately applied, would not only expel the child, but also lift up the mother, the accoucheur, and the nurse, all at once. It would be dangerous not only to the mother and child, it would imperil also the obstetrician. It has been calculated that if this force were applied just as the chief resistance to delivery was overcome, the child would be shot out of the vagina at the rate of 36 ft. per second."

Nobody has dared to challenge Duncan's estimate, and very few people have made any further investigation on the subject. One of the best studies was made by Wylie[7] in 1935. He used an ingenious device called a tractionometer (figure 4) incorporated into a Bill axis traction handle. By this means, he compiled some very interesting data on the forces used in forceps delivery. Traction was exerted

with each uterine contraction, and the force used to just advance the fetal head was recorded. The average force multiplied by the number of pulls gave the "resistance index." Wylie found that a low forceps extraction in the primigravida required an average of three pulls of 30 lb. each, or a total of 90 lb. A midforceps extraction in the primigravida required an average of five pulls of 42 lb. each, or a total of 210 lb., which is more than twice as much force as is required for low forceps extraction. Low forceps extraction in the multigravida required an average of two pulls of 22 lb. each or a total of 44 lb., and midforceps extraction required an average of three pulls of 35 lb. each, or a total of 105 lb. As in the case of the primigravida, midforceps extraction required twice the force required by low forceps extraction. Regarding the natural forces required to effect delivery, Wylie[7] said: "The amount of spontaneous effort required would at least be proportional if not equal to that recorded by forceps and tractionometer."

My observations with the tractionometer have confirmed those made by Wylie. The tractionometer makes it very evident that if the resistance offered by the pelvic floor and perineum is not reduced by intermittent stretching by the fetal head, as is accomplished by the head reaching the low station, the amount of traction and the number of pulls are markedly increased. An episiotomy will help somewhat, but only when the head is well onto the pelvic floor. Pulls of 75 lb. or more occasionally may be required to advance the head on the pelvic floor before "ironing out" or episiotomy or both have reduced the resistance.

Conservatism and patience, therefore, must be exercised in the use of forceps and in the management of difficult labor in general. If the mother and fetus are in good condition, and if the labor is not unduly prolonged, it is well to remember that patience saves patients, and that if the obstetrician is tired of waiting, the patient is more tired, and that it is perhaps best for both to take a rest.

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An amelanotic malignant melanoma is difficult to recognize. A lesion without much pigment may be mistaken for an inflammatory condition. Pigmentation occurs more often in malignant melanomas of the skin than in those of the mucous membranes. Diagnosis must be based on histologic examination. Skin-colored lesions of recent development, particularly on the toes, should be routinely subjected to biopsy.

Amelanotic Malignant Melanoma

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In the past few years here has been an increasing number of reports on malignant melanoma. The physician should be alert to the possibility of this condition even when circumstances appear to make it unlikely. While malignant melanoma is more likely to be considered in the differential diagnosis of a black or brown pigmented lesion, it must be remembered that some lesions are amelanotic. The absence of pigment or the odd location may be deceiving, especially to the untrained eye. The two case reports which follow illustrate such a situation.

Case Reports

Case 1—A 58 year old white woman had a lesion on the big toe of her right foot. One year earlier she had had a so-called ingrown toenail, nonpigmented, but with inflammation and discharge. At first she was treated by a chiropodist, who removed part of the nail. When the area failed to heal, she consulted a number of physicians, all of whom treated the condition as an infection. In addition to treatment with locally applied medications, the involved area was literally whittled away by excision or by curettage. The inflammation and discharge persisted. The condition was finally diagnosed as osteomyelitis, since the bone was exposed. At no time was a biopsy performed, nor was any roentgenographic examination made. The patient felt no pain or discomfort, the only symptom being a discharging lesion.

Examination revealed a rough, irregular partial amputation of the big toe of the right foot, extending back to the area of the nail matrix. The exposed surface was white, irregular and pebblelike, with no bleeding points. The exposed end of the bone was visible. There was no local tenderness or pain on motion. No glands were palpable in the groin or in the popliteal space.

Biopsy indicated that the lesion was an amelanotic melanoma, and operation was advised. The patient sought other opinions, and, after about a month's delay, she was hospitalized and the toe was amputated. Palpable glands removed from the groin area showed

"carcinoma, anaplastic, metastatic." The toe lesion was described as a "necrotic inflammation." Within three weeks massive nodes had developed in the patient's right groin; in time enlarged nodes developed in other parts of the body. There was progressive deterioration of her health, and she died within nine months.

Case 2—A 51 year old white woman was first seen in March 1949. Three months earlier, what she described as an area of irritation had developed on the dorsum of the right fourth toe. She thought the lesion had resulted from wearing a tight shoe. The area had turned a dark, dusky red-blue and had become purulent and painful. She was treated by a chiropodist, and the inflammatory process healed. However, drainage from the toe continued. There was no pain or tenderness, and no glands were palpable.

Examination revealed a swollen toe with an overgrowth of white friable tissue on the dorsum. There was no tenderness or restriction of movement. No nodes were palpable. Report of the biopsy examination was amelanotic malignant melanoma.

The patient was hospitalized, the toe was amputated, and all the nodes in the inguinal and femoral areas of the right side were excised. Microscopic examination of the tissue did not show any disease in the nodes.

The patient did well for the next four years, except for edema of the leg. She was seen routinely at regular intervals with no sign of recurrence. In October 1953, two dark black, pinhead-sized, slightly elevated lesions suddenly developed on the anterior aspect of her right midthigh. These were excised and reported as malignant melanoma. There were no other lesions or masses. In April 1954, two similar lesions developed near the previous site of operation. Quite suddenly, deep massive glands also developed in the right groin. The skin lesions were again reported as malignant melanoma, and an excised mass from the groin was described as melanosarcoma.

Over a period of months, an increasing number of stony, deep enlargements formed in various parts of the patient's body, particularly in nodes and deep skin tissues. These masses were most outstanding on her back and arms and, especially, in the thyroid area. In November 1954, scattered dark pigmented lesions were noted on her face and back. She failed rapidly and died in December 1954. Postmortem examination revealed a generalized involvement of all internal organs, including the heart, spleen, liver, kidneys and omentum.

Discussion

Clinical recognition of amelanotic malignant melanoma is difficult. In the beginning, the amelanotic lesion is often the same color as the skin, and, as Conway[1] has stated, diagnosis must be based on histologic examination. According to McGovern,[2] a lesion without much pigment may be mistaken for an inflammatory condition. Ewing[3] has said that amelanotic melanomas resemble unhealthy granulation tissue. Andrews[4] has stated that the degree of malignancy of nonpigmented melanomas is about the same as that of the pigmented variety. In most instances, melanoma arises from previously existing, apparently benign pigmented or nonpigmented nevi.[5] Pigmentation occurs more often in malignant melanomas of the skin than in those of the mucous membranes; in the latter site, the tumors lack pigmentation in about one-half of the cases.[6,7] Allen[7] found no correlation between intensity of pigmentation of the primary tumors and such factors as length of patient's survival, pleomorphism, number of mitotic figures, inflammation and ulceration. In his series of 362 cases of malignant melanoma, he reported pigmentation of varying amounts in 79 per cent of the cutaneous tumors and in only 54 per cent of the primary melanomas of the mucous membranes. He also stated that cutaneous metastatic lesions from melanoma of the eyes often are nonpigmented, as are rapidly spreading malignant melanomas starting in the skin with distant cutaneous and internal metastases. Conway[1] observed that metastases from a pigmented melanoma may not show pigmentation, but occasionally metastases from an amelanotic melanoma may be pigmented.

Differential diagnosis—Wright[8] believes that delay in proper management of subungual lesions is due to errors in the differential diag-

nosis of paronychia, granuloma, chancre, mycoses, melanosis, epidermoid carcinoma, etc., along with correspondingly erroneous histologic diagnoses. Anaplastic squamous cell carcinomas, which alone are likely to be confused with melanoma, are never pigmented, according to Lennox.[9] He also stated that occasionally melanin can be demonstrated in a clinically pigment-free lesion by using the silver reaction. Fanger and Roberts[10] have observed that the great variety of histologic patterns presented by malignant melanoma makes it important to include this disease in the histologic differential diagnosis of neoplasms, such as fibrosarcoma of the lower extremity, even in the absence of pigment. A careful search for melanin pigment is required. Ewing[3] observed that lesions which simulate malignant melanoma include infected pigmented basal cell epitheliomas, infected pigmented papillomas, benign hairy moles and glomic tumors.

The primary lesion from which malignant melanoma is likely to develop is a flat mole, varying in color.[11] Bleeding and itching often occur.[3] Growth of the mole is the most frequent sign of activity.[11] Late signs of activity are irritation, infection, bleeding and ulceration. There may be change in color, with formation of a red areola, caused by increased vascularity around a lesion without much pigment; this may be mistaken for an inflammation.[2] These changes are often related to trauma.[8,11-13] Allen and Spitz[6] believe that there is no evidence that ulceration accelerates the growth of a melanoma resulting from trauma or inflammation. Shaffer[14] stated that no lesion proved histologically benign has ever been recorded as degenerating into a malignant melanoma after partial removal. Development of metastases in the regional nodes or in the distant viscera may cause the first symptoms the patient himself notices.

In retrospect, our two cases fall into a number of categories previously discussed. Both patients were women in the 50 to 60 year age group. In each a nonpigmented lesion developed in a toe, and in each case the proper diagnosis was not established until later. Each had ulceration as a prominent sign, the diagnostic significance of which was not recognized. In each case the toe was amputated. In the first case, only the palpable nodes were removed. Even though the nodes were considered to be metastatic lesions, no attempt was made to remove all of them. Massive nodes developed in this region within weeks. The first report on the toe tissue in one case was either apparently in error or proper tissue had not been submitted for examination, thus bearing out Becker's[15] report on pitfalls in diagnosing malignant melanoma. In the second case, all nodes were removed, and the patient remained well for over four years. The new lesions which developed were pigmented, in contrast with the original nonpigmented lesion. These new lesions might have been new primary foci, as described by Pack, Scharnagel and Hillyer.[16] Toward the end, the patient had superficial pigmented lesions. Postmortem examination showed the type of extensive involvement of internal organs described by Pillsbury, Shelley and Kligman.[17]

Each case presented a problem of management. Radical surgery was considered but discarded in favor of conservative and limited procedures. In the first case, the course was rapid, with death occurring within two years after onset of the disease. The second patient survived five years.

These cases have been presented to show the course of primary nonpigmented malignant melanoma. Apparently innocuous lesions were not identified correctly until some time had passed. The earlier the recognition and extirpation of such lesions, the better the prognosis, although it is usually serious in any event. Skin-colored lesions of recent development, particularly on the toes, should be subjected to biopsy routinely, because they well may represent melanotic malignant melanoma.

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Postgraduate Clinical NOTES

121. THE AGEING SKIN

The menopause certainly marks a stage in life; this stage may be erratic in course and duration. Dermatologically speaking it is a stage when the signs of ageing of the skin tend for the first time to become obvious and women more avidly than ever before lap up the tips from the beauty queens who write so enthusiastically in the weeklies and monthlies on the care of the skin and at whose very word of command the pores open and close. The skin at this time is becoming thinner, in the first place because of decreased thickness of the horny layer. Some change in the formation of keratin leads to the scaling of the skin becoming more visible. There is less water held in the horny layer. The amount of secretion from the sebaceous glands lessens. As the damaging effects of alkali on the skin are due to a chemical and physical disturbance of the horny layer, the thinner and the more emaciated the horn the more likely is it to suffer in this way. Chapping and fissuring of the skin of the hands from these effects of alkali therefore may well first be a trouble at this time. It is, of course, comforting for a woman to be able to blame her "housewife's hands" on a detergent rather than have to admit to age and its debilitating effect on the skin, but if used in sensible concentrations and with the obvious precautions detergents would rarely cause trouble.

David I. Williams, The skin and the menopause, *Practitioner*, May 1959, pp. 574-577

Effect of Competitive Industrial Activity on the Traumatic Paraplegic

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A detailed medical study of 10 paraplegic employees of an electronic manufacturing plant indicates that competitive industrial activity and adequate medical care are beneficial in restoring body function and a more normal living pattern and preventing most of the usual complications. The average duration of paraplegia in this group was 18.2 years. There were no compensable accidents during their employment, which represented a total time of more than 36 years. The rate of absenteeism was low. The traumatic paraplegic is a competent, safe worker.

TRAUMATIC paraplegia is an increasing civilian problem. The United States Public Health Service has estimated that as of 1953 there were 100,000 paraplegics. A high percentage of these persons have been retrained to live productive lives through proper rehabilitation services.[1]

Statistics on longevity of persons with paraplegia differ greatly. Guttermann and associates[2] reported a mean survival time of about 28 to 30 months after onset of the condition. A report from Australia[3] gives the average longevity as three years and records two cases in which the patients survived 32 and 33 years respectively. Talbot and Lyons[4] reported a mean survival time of 68 months in their series. Dietrick and Russi,[5] in a review of 55 cases, gave the life span as only 52.8 months from the time of injury and noted that the average survival of paraplegic persons dying before 1950 was 34.9 months compared with 71.3 months for those dying after 1950. They concluded that a person becoming paraplegic today has a better life expectancy than he would have had 10 years ago, and that the figures now available indicate too short a life expectancy for paraplegic persons.

Study of 10 Paraplegics Employed in Industry

We made a detailed medical study of 10 paraplegic persons employed at Abilities, Inc., Albertson, Long Island. The work is highly skilled electronic manufacture, and the employees are subjected to the usual rigors of competitive industry; in addition to the strain of activities of daily living, there are the mul-

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tiple pressures of traveling to and from work, meeting production schedules, and engaging in a more active social sphere.

Data relative to pre-employment medical history, present physical findings, and changes in physical and emotional components were correlated with the increase in activities and exposure to usual physical hazards as seen in active industry. The type of work each employee performs, the rate of absenteeism, compensable accidents, and mode of travel to and from work were listed and evaluated.

Table 1 describes the disabilities of the 10 employees and gives their age, sex, type of work, and mode of travel to and from work. Each employee works from a wheel chair. All drive their own cars except W. B., who uses a car pool. Three are able to walk with leg braces and crutches for short distances only; the other seven are confined to wheel chairs. On the job, however, all work from wheel chairs only. Two of the employees have some control of rectal and bladder function, and two others have either bladder or rectal control. Six have histories of recurrent decubitus ulcers since their accidents, and three of these six persons had actively draining sinuses and decubitus ulcers and positive urine cultures at the time of employment. Four have histories of urinary tract calculi. The average travel time to and from work is one hour and four minutes, and the average distance is 31.4 mi.

The length of employment at the time of examination ranged from three months (W. B.) to six years (L. S.) (table 2). These workers represent a total time of employment of 36 years and three months, with an average of 3.6 years. Absenteeism totals 92 days and 10 and one-half hours, the average time lost being 9.3 days. The compensable accident record is zero.

Table 3 summarizes the previous rehabilitation, unemployment and complications. These 10 employees represent a total of 11 years of formal rehabilitation, for an average of 1.1 years each, but it should be noted that five had not had rehabilitation. The period of unemployment since the onset of the disability ranged from no unemployment to nine years. Only three of the workers were employed continuously after their accidents. The other seven were unemployed for from two to nine years.

Since employment, six of the 10 workers have not had any change in their original condition, three have shown improvement, and only one has had further deterioration of decubitus ulcers (L. S.).

Complications of traumatic paraplegia were present at the time of employment in all cases except one. Obesity and hypertension were present in two, active decubitus ulcers in three, muscle spasms of varying severity in five, genitourinary infection in two, bladder stones in two, and contracture deformity in two; the latter occurred after employment. No instances of amyloidosis, cirrhosis of the liver, or other complications noted in the literature were found. In only one case have complications developed since employment (L. S.), and they consisted of a bladder stone in 1956 and fixation of the knee at 20 degrees of flexion. This same employee had severe deterioration of decubitus ulcers, with osteoporosis and osteomyelitis, and had to be hospitalized. Decided improvement of muscle spasms occurred in two cases, in one patient after three and one-half years and in the other after five years of employment.

Report of Cases

J. W.—This 43 year old man was examined in November 1957. He was employed in August 1952. In 1950, while working as a deep-sea diver, he had severe caisson disease. Decompression was not immediately obtainable and was instituted one week later. The lower extremities were paralyzed except for slight muscular response (approximately 10 per

TABLE 1

DATA ON 10 PARAPLEGICS EMPLOYED IN AN ELECTRONIC MANUFACTURING PLANT

EMPLOYEE, AGE AND SEX	TYPE OF WORK	DISABILITY	MODE OF TRAVEL, ONE-WAY TRAVEL TIME AND DISTANCE
W. B., 52, M	Bench work, electronic	Traumatic paraplegia in 1947. Walks with aid of crutches and braces. No muscle wasting. Partial bladder, rectal control. Blood pressure 184/104. Obesity	Car pool; 45 minutes; 25 mi.
A. C., 58, M	Harness worker	Spinal cord injury in 1905 at age of five years. Left leg affected mostly. Walks with a hip-swinging gait and drags left leg, which exhibits greater muscle wasting than the right. Normal bladder-sphincter control. Blood pressure 150/104. Moderately obese	Drives; 20 minutes; 6 mi.
C. D., 35, M	Mechanical drill press	Spinal cord injury in 1944 at D10. Confined to wheel chair. Loss of all movement and sensation of legs. Wasting marked. No bladder or rectal control. Left lateral lumbar scoliosis. Occasional decubiti	Drives; 30 minutes; 11 mi.
R. K., 36, M	Section foreman	Spinal injury in 1944 at D9. Complete loss of function and sensibility of legs. No bladder or rectal control. Draining sinus of lower back. Four plus edema of ankles. Both legs slightly atrophic, left more than the right	Drives; 30 minutes; 10 mi.
H. M., 39, M	Bench work	Birth injury to spine and possible poliomyelitis at one and one-half years of age. Complete paralysis of legs and flexion deformity of knees (fixed at 80 degrees). Marked right dorsolumbar scoliotic deformity with narrowing of left chest. Marked atrophy of the legs. No bladder or rectal control. Blood pressure 170/110	Drives; 25 minutes; 14 mi.
J. Pi., 42, M	Inspector	Spinal injury in 1948. Complete paralysis of both legs. Four plus edema. Bladder control 2 plus. No rectal control. Recurrent decubiti	Drives; 25 minutes; 10 mi.
J. Po., 35, M	Coil winder	Multiple injuries including spine in 1947. Patient was taught crutch balance and brace walking. No muscle wasting. Normal sensation in legs. No bladder control. Rectal control 4 plus. Recurrent decubiti	Drives; 40 minutes; 25 mi.
J. W., 43, M	Methods engineer	Caisson disease in 1950. Paralysis of legs with retention of superficial sensation. No bladder or rectal control. Traumatic blindness of the left eye. No atrophy. Recurrent decubiti	Drives; 25 minutes; 14 mi.
H. C., 56, M	Bench work, electronic	Spinal injury in 1950 at D10 and D12. Complete paralysis of legs. Braces on legs (long on right leg, short brace on left). Can use crutches. Normal reflexes. No bladder or rectal control	Drives; 25 minutes; 12 mi.
L. S., 40, F	Typing and clerical	Spinal injury in 1944. Complete paralysis of legs. Decubiti of lower spine and buttocks. Moderate atrophy of both legs, with knee flexion fixed at 20 degrees. No bladder or rectal control	Drives; 60 minutes; 30 mi.

TABLE 2

LENGTH OF EMPLOYMENT, ABSENTEEISM AND ACCIDENT RATE

EMPLOYEE	LENGTH OF EMPLOYMENT AT TIME OF EXAMINATION	ABSENTEEISM	COMPENSABLE ACCIDENT RATE
W. B.	Three months	Two days	None
A. C.	Five years	Three days	None
C. D.	Six months	None	None
R. K.	Three and one-half years	One day, one and one-fourth hours	None
H. M.	Four years	One day	None
J. Pi.	Four years	Twenty days; six hours	None
J. Po.	Four years	Fifteen days, three and one-fourth hours	None
J. W.	Five years	None	None
H. C.	Four years	Twelve days	None
L. S.	Six years	Eleven days; 38 day leave of absence	None

cent) of both quadriceps. All sensations in the legs were absent except for superficial tactile response of both thighs. Loss of bladder and rectal control was complete. The patient was hospitalized for two years and was completely wheel chair-bound. In February 1952 he had bladder stones and urinary infection. He had not had any formal rehabilitation. He was depressed and felt completely useless. After the bladder stones were removed, he was employed at Abilities, Inc. in August 1952.

His job as methods engineer kept him busy and active. Although confined to a wheel chair, he learned to walk with crutches, with a four point gait, and began to take active corrective exercises. In 1955 a urinary bladder infection developed which responded well to therapy. In 1957 he was hospitalized and an attempt was made to break up the spinal cord adhesions by intrathecal catheterization. A Knight spinal brace and leg braces were advised to increase his crutch-walking time. A series of specific exercises were recommended, and some function of the tibialis anterior muscles returned. The peroneal muscles also showed some traces of power, and quadriceps function has increased to about 25 per cent. Bladder and rectal control was still absent and urinary catheterization was still necessary.

J. W. is now very active at work and is interested in his outside activities; he has begun to sail a boat as a hobby. In July 1958 he married a polio quadriplegic.

No complications have been noted to this date except for the previously mentioned *Proteus* infection of the urinary bladder in 1955. All subsequent urinary cultures have been negative.

L. S.—This 40 year old woman was employed at Abilities, Inc. in November 1953. In 1944 she fractured her spine at L3. Paralysis of the legs and loss of bladder and rectal control resulted. Severe decubitus ulcers developed around the buttocks and on the lower part of the back, and plastic surgical procedures were performed in 1947, 1948, 1950 and 1951. The ulcers healed temporarily and began to break down again in 1953, before employment. Both knees were fixed at 20 degrees of flexion, and the legs were atrophied. She was employed in November 1953. The decubitus ulcers did not heal, and began to extend. A bladder stone developed in 1956 and was removed in July 1956. Osteoporosis of the lower extremities was present. The patient refused all treatment. Osteomyelitis of the left hip developed and she was sent to the hospital for surgical treatment on November 18, 1957.

Comment—Definite deterioration occurred with resultant complications of decubitus ulcers, bladder stones and infection, osteoporosis, osteomyelitis, knee ankylosis, and leg atrophy. This woman, although employed, was negligent in therapy and persisted on an inadequate diet contrary to advice. While in the hospital, the proper diet and medical and surgical care resulted in control of the osteomyelitis, healing of the decubitus ulcers, and a weight gain of 30 lb. She is now back at

TABLE 3

PREVIOUS REHABILITATION, UNEMPLOYMENT, AND COMPLICATIONS

EMPLOYEE	PREVIOUS REHABILITATION	PERIOD OF UNEMPLOYMENT SINCE DISABILITY	DEGREE OF CHANGE	COMPLICATIONS WHEN EMPLOYED	COMPLICATIONS SINCE EMPLOYMENT
W. B.	Six to nine months	None	None	Obesity, hypertension	None
A. C.	None	None	None	Obesity, hypertension	None
C. D.	Nine months	Ten years	None	Decubiti on back corrected with skin grafts	None
R. K.	Seven years	Seven years	Thirty per cent improvement in function and general health. No more muscle spasm	Decubiti, ankle and knee sores, all corrected except for recurring draining sinus over buttocks. Chronic urinary infection. Muscle spasms 3 plus, urine 1 plus	None
H. M.	None	None	None	Essential hypertension. Cystic hygroma of neck removed February 1953. Scoliosis of spine. Fixation of knees in 80 degrees of flexion. Coarse tremor of legs on passive motion. Muscle spasm 1 plus	None
J. Pi.	None	Five years	None	Bladder stone removed before employment. Edema of both legs	None
J. Po.	One and one-half years	Six years	None	None	None
J. W.	None	Two years	Improvement in leg function attributed to therapy, with muscle spasm, approximately 2 plus	Bladder stone removed in 1952. Muscle spasms 4 plus, urine 1 plus	None
H. C.	One year	Three years	Improved generally; 20 per cent increase in leg strength, improvement in navigation	Bladder stone removed in 1951. Muscle spasms 1 plus	None
L. S.	None	Nine years	Deterioration of decubital ulcers requiring hospitalization and surgery	Decubital ulcers. Muscle spasms 2 plus	Bladder stone, 1956. Fixation of knees, 20 degrees of flexion. Osteomyelitis and osteoporosis

work and cooperatively attending to her hygiene and diet.

Complications of Paraplegia

The literature on complications of chair-bound paraplegics is voluminous, especially in regard to disorders of the kidneys (infection and stones), decubitus ulcers, contractures and, recently, other chronic diseases such as amyloidosis, cirrhosis of the liver, and vascular degenerative diseases[6] which are being recognized as causes of death. The most frequent complication is still listed as urinary tract disease.[7]

Urinary calculi commonly complicate paraplegia and are due to loss of calcium in the long bones of the legs because the patient remains in a sitting or lying position. One hour of standing daily will keep the calcium in the long bones and help prevent urinary calculi.

Conarr[8] stated that four urinary complications generally occur, early or late: vesicoureteral reflux, renal or bladder calculosis, penoscrotal fistula or diverticulum, and epididymitis. He also said that in nearly every case, culture of the urine shows bacteria, and there are leukocytes in the urine whether a catheter is present or not. This infection usually is well tolerated because eventually local tissue immunity develops.

Amyloidosis as a complication of traumatic paraplegia was first reported in 1867, but it was not until 1949, when Thompson and Rice[9] reported four cases, that it was suspected that this complication was a frequent occurrence. Since then numerous publications[10-12] have stressed the association of pyelonephritis, decubitus ulcers and urinary tract infections as the most likely causes of this deadly complication of paraplegia.

Decubitus ulcers follow when there is interference with local circulation of sufficient degree and for a sufficiently prolonged time. This complication of paraplegia is next in frequency to urinary tract disease. There are many theories as to the cause of these ulcers. Shearing force of raising from a supine to a sitting position or turning in bed causing compression of skin and subcutaneous tissues between unyielding bone on one side and a firm mattress on the other has been noted as a factor in producing these ulcers.[13]

Localio and associates[14] reported a study on nonhealing decubitus ulcers in 11 patients with traumatic paraplegia and found that the most important factor in nonhealing was reinjury or trauma to a denervated area. Because of lack of pain sensation, the patient cannot protect himself against the destructive effects of local pressure ischemia.

Autonomic hyperreflexia is manifested by sweating of the forehead, cutis anserina, nasal obstruction and severe headache, and is accompanied by a high systolic and diastolic pressure with bradycardia. This syndrome occurs only with lesions above the sympathetic outflow to the abdominal viscera. More than 80 per cent of persons who have quadriplegia present this phenomenon. Various stimuli will set off this reflex, such as tactile and thermal stimulation of the skin and visceral distention or contraction. The viscus most often responsible is the urinary bladder, with the rectum next in order. Complete investigation of these viscera should be made if this phenomenon is found. Postural hypotension also may be observed in patients with this syndrome.

Paraplegic persons often exhibit marked atrophy of the unaffected upper extremities from disuse or malnutrition. Specific exercises or activity can prevent this complication, with special precaution to prevent spinal flexion or hyperextension. Particularly important are activities which strengthen the triceps and finger flexors, since these muscles are essential in crutch walking.

Cooper and Hoen[15] have shown that a negative nitrogen balance can occur early in traumatic paraplegia; it re-establishes itself to normal in 8 to 10 weeks after the injury. They also stressed the occurrence of impaired liver function, decrease in basal metabolic rate, unilateral or bilateral mammary enlargement in 20 per cent of male patients, testicular atrophy in more than 50 per cent, and cessation of menses for three to six months in young adult females.

Dr. Howard A. Rusk,[16] in his book titled "Rehabilitation Medicine," has written an excellent chapter on rehabilitation of the patient with paraplegia or quadriplegia. The advice as to specific exercises, hygiene, bladder care, and prevention of other complications is clearly stated and should be followed *by* the paraplegic person all his life.

Of the recorded complications cited in the literature, we encountered only *three cases* of decubiti in this group of 10 employees, and of these three only one developed after employment. Urinary calculi developed in only one case (L. S.); because of personal neglect, this patient had severe decubiti and osteomyelitis requiring hospitalization. Two of the

workers were found to have positive urine cultures; the infections were controlled quickly with antibiotics and chemotherapeutic measures. No instance of amyloidosis, liver cirrhosis, vascular degenerative disease, severe osteoporosis, atrophy of upper extremities, spinal flexion or hyperextension, or metabolic insufficiency was found.

Comment

The longevity statistics cited at the beginning of this report certainly are not applicable to this group of paraplegic persons, in which the average duration of paraplegia is 18.2 years without any deaths.

It is quite evident from the factual data presented that the increase in physical effort which occurs during employment can prevent most of the common complications of paraplegia, prolong life, and restore a more normal pattern of living. The absence of compensable accidents in this group of workers may be startling to some, but this is a general finding at Abilities, Inc. and shows that work exposure, as practiced in industry, poses no physical hazard to the disabled. The excellent record in regard to absenteeism may reflect better general health as a result of competitive work effort.

Conclusion

Competitive industrial activity coupled with adequate medical care appears to be a beneficial factor in restoring normal body function and inhibiting the development of the usual complications of the sedentary traumatic paraplegic. The traumatic paraplegic is a competent, safe, reliable worker.

Addendum

A paraplegic man who had been an employee of Abilities, Inc. but had been laid off because of a temporary cutback was rehired after this report had been prepared. Originally employed in April 1956, and examined in November 1957, this 25 year old man gave a history of traumatic paraplegia resulting from an automobile accident in September 1940. He had complete paraplegia of the lower extremities, loss of bladder and rectal control, lower thoracic and lumbar scoliosis of marked degree, and flatness of the left chest wall because of spinal distortion. He took GANTRISIN® from time to time for a chronic cystitis. He had not been able to stand erect in spite of braces and rehabilitation at New York University-Bellevue Medical Center. His record of absenteeism consisted of a one month leave of absence and seven days lost from work for other reasons (three days because of travel difficulties and four days because of illness). He traveled 34 mi. one way, which took about an hour.

This man was employed at bench work until he was laid off in March 1958. He was rehired July 7, 1958. During this time there were no complaints, nor was there any indication of complicating diseases. On November 7, 1959, he left work at the usual time, 5:30, and while driving out of the parking lot was suddenly seized with severe chest pain. Cyanosis developed rapidly. He did not respond to artificial respiration in a respirator, and he died within half an hour while being taken to the hospital in an ambulance. Autopsy revealed a large pulmonary embolism from an unnoticed phlebothrombosis of the leg.

Comment—Although pulmonary artery embolism with infarction is mentioned in the literature, few authors list this condition as a cause of death. Dietrick and Russi[5] reported two cases of pulmonary infarction as a cause of death in 55 autopsies (3.6 per cent). Rusk, in his primer for paraplegics and quadriplegics,[17] mentions the use of elastic bandages for edema of the feet and the use of pillows to elevate the feet when the patient is in bed. This reduces the stasis which is so frequently present, and helps prevent phlebothrombosis.

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CLINICAL STUDY

Chymotrypsin; Clinical Pharmacologic Evaluation as an Anti-inflammatory Enzyme

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Extensive studies have been conducted to compare the effect of the enzyme chymotrypsin with that of other anti-inflammatory drugs. The authors' investigation showed chymotrypsin to be more effective than were anticoagulants in treating acute thrombophlebitis. The course of treatment of inflammation of the eye was shortened by use of chymotrypsin in conjunction with neomycin-polymyxin. The effect of chymotrypsin exceeded that of trypsin and paralleled that of prednisone in treating bruises and sprains, while hematoma responded more quickly to chymotrypsin than to either of the other two agents. The authors also suggest that chymotrypsin may be valuable in other inflammatory conditions.

A REVIEW of the many articles reporting the beneficial effect of anti-inflammatory drugs (steroids, etc.) reveals that these drugs cause many untoward reactions, including peptic ulcer, hypertension, Cushing's syndrome, and psychopathologic changes. As a result of these observations extensive investigation has been made to discover safer anti-inflammatory agents that would have a broad field of clinical application.

OSCAR F. DAVIS

Studies with trypsin indicated that proteolytic enzymes might afford anti-inflammatory action as well as a fibrinolytic action.[1-3] Based on these observations, the enzyme chymotrypsin was crystallized, and investigation of its biologic activity was begun. Extensive studies were undertaken in order to compare the effect of this proteolytic enzyme with that of other anti-inflammatory drugs.

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Pharmacology of Chymotrypsin

The pharmacologic action of chymotrypsin has been summarized as follows.[4,5]

In order to determine the anti-inflammatory action of chymotrypsin, inflammation was induced by injecting 0.1 cc. of 10 per cent, 30 per cent and 50 per cent concentrations of turpentine in oil under the plantar aponeurosis of guinea pigs. Subsequently, a solution of chymotrypsin in sesame oil was injected subcutaneously at another site. The anti-inflammatory effect of the chymotrypsin was determined by means of the decrease in weight of the affected paw after the injection of this enzyme. This investigative study was controlled in the following manner: (1) by the injection of sesame oil alone, (2) by the injection of trypsin in doses containing the same number and twice the number of units contained in the doses of chymotrypsin, (3) by the injection of 20 mg. of cortisone acetate per kilogram of body weight, (4) by the injection of 100 mg. of sodium salicylate per kilogram of body weight, and (5) by adrenalectomy. On a unit to unit basis, the anti-inflammatory effect of chymotrypsin was at least twice as great as that of trypsin, and it also was greater than that of the cortisone acetate and the sodium salicylate.

Administration of chymotrypsin reduced the anaphylactoid inflammation that had been induced by the intraperitoneal injection of dextran. This effect was measured by a decrease in the weight of the animals after the administration of the chymotrypsin.

Forelegs of animals were treated with sesame oil and paraffin, and chymotrypsin was administered subsequently. The average weight of the forelegs that had been treated with sesame oil was 478.7 mg. and that of the forelegs that had been treated with paraffin was 487.5 mg. After the administration of chymotrypsin, the average weight of the forelegs that had been treated with sesame oil was 426.2 mg. and that of the forelegs that had been treated with paraffin was 403.5 mg.

Chymotrypsin is a more effective proteolytic agent than trypsin. It causes lysis of fibrin more rapidly, and with a lower concentration. It does not cause blood clotting. This is in contrast to trypsin, which activates prothrombin to thrombin. Indeed, chymotrypsin prolongs the clotting time and has a heparinlike action in activating the conversion of profibrinolysin (plasminogen) to fibrinolysin (plasmin). Necropsy did not disclose any evidence of intravascular thrombosis in 33 animals that had received large doses of chymotrypsin.

Chymotrypsin is one-fourth as toxic as trypsin, which itself is weakly toxic. Chymotrypsin does not cause any of the profound effects on metabolism that commonly are observed after the administration of therapeutic doses of steroids. It does not enhance the spread of infection. The mechanism of its antiedemic and anti-inflammatory action apparently differs from that of the steroids.

Materials and Methods

Because of the clinical needs discussed, and because of the statistically significant results (as measured by chi square, probability, and Probit analysis) obtained by administration of chymotrypsin to animals, an investigation of the effect of this enzyme on human beings seemed to be indicated. In undertaking this study, we were cognizant of several serious limitations, which seem to attend most clinical studies. The pharmacodynamics of the compound in the experimental animal cannot be extrapolated into clinical facts. A more serious limitation is that the investigator has only meager ability to measure precisely the effect of the compound on human pathology.

One hundred and eighty-four cases were considered in this study. All of the patients were adult men and women. The cases were divided into two groups, namely, a group of 112 cases in which chymotrypsin was used alone, and a group of 72 cases in which chymotrypsin either was not used or was used in conjunction with other medicaments. The latter group was used as a control. In selecting the cases in which chymotrypsin was to be used, a cautious attempt was made to exclude cases in which drugs were being administered for conditions other than those for which the chymotrypsin was to be administered.

The group of 112 cases in which chymo-

trypsin was administered alone included 32 cases of inflammation (24 cases of acute infectious conjunctivitis and 8 cases of acute iritis), 40 cases of trauma (22 cases of sprains or bruises and 18 cases of hematoma, including hematoma of the eye), and 40 cases of either thrombophlebitis or phlebothrombosis (table 1).

The group of 72 cases in which chymotrypsin either was not used or was used in conjunction with other medicaments included 21 cases of conjunctivitis, 16 cases of trauma, 20 cases of thrombophlebitis or phlebothrombosis, and 15 cases of infected wounds. Chymotrypsin was used in conjunction with neomycin-polymyxin ophthalmic in eight of the 21 cases of conjunctivitis, and it was used in conjunction with chemotherapeutic agents in all of the 15 cases of infected wounds (table 1). The patients in this group of cases did not know the type of medication that was used, and in all but a few of these cases the investigators did not know whether or not chymotrypsin had been used.

In the cases in which chymotrypsin was used, 1 cc. of a saline solution of this enzyme (CHYMAR® aqueous) was administered once a day for at least four days. The patients were observed for at least 10 days after treatment was discontinued. By this means we were able to estimate the relapse rate more accurately and to detect the occurrence of masked beneficial results.

Results

The results of treatment in the two groups of cases are summarized in table 1. Although the therapeutic measures employed in the control group of cases are by no means complete, a comparison of the results obtained in this group and the results obtained in cases in which chymotrypsin was used alone does offer some corroborative evidence of the effectiveness of this enzyme. Biostatistical evaluation of the data obtained (chi square, probability and Probit analysis) indicates that the results obtained with this enzyme, especially in the cases of trauma and thrombophlebitis (and phlebothrombosis), were not a consequence of chance.

Comment and Conclusions

A comparison of the results obtained with chymotrypsin in thrombophlebitis and in phlebothrombosis and the results obtained with DICUMAROL® and those obtained with saline packs and rest in bed suggests that this proteolytic, anti-inflammatory enzyme produces a measurable degree of benefit. The response produced by this enzyme seems to result from two mechanisms: (1) a mechanism that acts immediately by depressing inflammation and by inhibiting further inflammation, and (2) a delayed mechanism of anticoagulation. Our study does not support the conclusion that the anticoagulant properties of chymotrypsin are equal to those of the classic anticoagulants. However, the moderate fibrinolytic and anticoagulant properties of this enzyme and its considerable anti-inflammatory property recommend it for further study in cases of thrombophlebitis. More extensive study, indeed, may support the need for powerful anticoagulants whose dose and hemorrhage-provoking influence may be decreased by the concomitant use of chymotrypsin. Our study seems to indicate that the acute stage of thrombophlebitis is less responsive to anticoagulants than it is to chymotrypsin.

In cases of inflammation, especially in those of the eye, the results obtained with the administration of chymotrypsin alone were compared with the results obtained with the administration of chymotrypsin in conjunction with neomycin-polymyxin ophthalmic and with the results obtained with the administration of the steroid prednisone ophthalmic. Neomycin-polymyxin was chosen after bacterial cultures and sensitivity tests had been made and because of the considerable breadth of antibacterial activity of these antibiotics. The results of this comparison suggest that the course of therapy was shortened in patients to whom chymotrypsin was administered in conjunction with neomycin-polymyxin ophthalmic. This perhaps may be attributable to the antiedemic and anti-inflammatory properties of chymotrypsin, or to the enhancement of the antibacterial properties of neomycin-polymyxin ophthalmic.

TABLE 1

CLINICAL INFLUENCE OF CHYMOTRYPSIN

PATHOLOGIC CONDITION	CASES	TREATMENT	SHORTENED CLINICAL COURSE; PROMPT AND MARKED REDUCTION OF INFLAMMATION AND DISCOMFORT	MEDIUM IMPROVEMENT IN SEVERITY OF INFLAMMATION AND DISCOMFORT	INDIFFERENT RESPONSE	INCREASED SEVERITY	UNTOWARD REACTION APPARENTLY ATTRIBUTABLE TO THERAPY*	RELAPSE WITHIN 10 DAYS AFTER THERAPY DISCONTINUED
In 112 cases in which chymotrypsin was administered alone								
Inflammation (32 cases)								
Acute infectious conjunctivitis	24	Chymotrypsin	18	3	3	0	0	0
Acute iritis	8	Chymotrypsin	4	2	2	0	0	0
Trauma (40 cases)								
Sprains or bruises	22	Chymotrypsin	14	4	4	0	2	0
Hematoma, including hematoma of eye	18	Chymotrypsin	11	3	4	0	0	0
Thrombophlebitis or phlebothrombosis	40	Chymotrypsin	26	7	7	0	2	0
In 72 cases in which chymotrypsin was not administered or was administered with other medicaments								
Conjunctivitis (21 cases)	8	Chymotrypsin and neomycin-polymyxin ophthalmic	8	0	0	0	0	0
	5	Neomycin-polymyxin ophthalmic	4	0	1	0	0	0
	8	Prednisone	5	1	1	1	0	2
Trauma (16 cases)	8	Trypsin	3	2	3	0	0	0
	8	Prednisone	3	1	4	0	0	0
Thrombophlebitis or phlebothrombosis (20 cases)	10	Dicumarol	0	0	0	0	1	0
	10	Saline packs and rest in bed	1	4	5	0	0	0
Infected wounds	15	Chymotrypsin and chemotherapy	9	4	1	1	0	0

*The untoward reaction was a mild eczematoid dermatosis.

There was no instance of spread of infection or a relapse in any of the cases in which chymotrypsin was used. This is in contradistinction to the cases in which steroids were used. Even in cases in which chymotrypsin was used alone, the edema, erythema and pain apparently were alleviated markedly and rapidly. One may conjecture that the selective inhibition of inflammation by chymotrypsin allows leukocytes to enter the field of infection but does not permit the entrance of other cells and edema fluid. Total inhibition of all of the components of inflammation would not be consonant with a shortening of the clinical course, which appears to have resulted from the administration of chymotrypsin.

The results of our study seem to indicate that the effect of chymotrypsin exceeds that of trypsin in the treatment of bruises and sprains and that it more or less parallels that of prednisone. Hematoma, however, seems more responsive to chymotrypsin than to prednisone or trypsin. In addition, the danger of infection in cases of trauma offers one argument, perhaps academic, against the use of steroids.

In the cases of infected wounds, the management of infection as well as the consequent wound healing apparently was aided by the use of chymotrypsin. This distinct impression is, however, a clinical one and is difficult to substantiate. This is because of the extreme hazards in measuring wound healing and inhibition of infection, and particularly in specifically attributing beneficial changes to a medicament that is used as an adjuvant to chemotherapy.

In conclusion, it should be emphasized that the mechanism of action of chymotrypsin is beyond our present knowledge. As a result of our study, we were encouraged to study this enzyme in the treatment of other inflammatory lesions, particularly peptic ulcer and chronic idiopathic ulcerative colitis. Our data regarding the effectiveness of this enzyme in the treatment of these lesions as well as in the treatment of rheumatoid arthritis and gout are, however, too meager for publication at this time.

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*The untoward reaction was a mild eczematoid dermatosis.

Self-help Devices:

Bathing Aids

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TODAY many commercially available devices make it possible for the disabled to achieve personal cleanliness when restriction of motion in the upper extremities interferes with the use of standard facilities such as washcloths, brushes, combs, etc. Even tub bathing, one of the most difficult problems, can often be managed with the help of special aids.

In this article, the first of a series on personal grooming, are illustrated devices that compensate for loss of reach and grip in soap-and-water activities. Subsequent articles will show (1) aids for transfer to and from a bathtub when a stall shower is not available or cannot be used, and (2) grooming aids for shaving, combing hair, applying lipstick, cutting nails, etc.

FIGURE 1. The washcloth-on-a-handle shown here covers a flexible rubber paddle, which is attached to a jointed wooden shaft that is angled for comfortable approach to the face. Available from Adjustics, 169 Thompson Street, New York, for approximately $2.50.

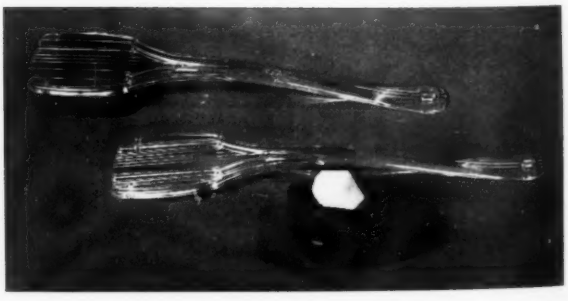

FIGURE 2. This plastic sponge-rubber bath brush is lightweight and offers increased reach; the pocket for retaining the soap eliminates the need for holding the soap and retrieving it should it fall out of reach. Available from Fascole, 229 Fourth Avenue, New York, for approximately $2.00.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

FIGURE 3a. The metal shaft attached to this rubber sponge provides additional length and the knurled plastic handle aids gripping. Available from Fascole for approximately $2.50. b. A cellulose variant with a replaceable head and a wooden shaft can be purchased from most Woolworth stores for approximately $1.00.

FIGURE 4. The REACH ALL® may be used for washing between the toes. Available from novelty and department stores for about $1.00.

FIGURE 5a. If grip and holding are major problems, a nailbrush which fits over the palmar surface of the hand offers a solution. b. The need to hold can be completely eliminated by this brush, which can be attached by suction to the wall at a comfortable height or to the sink. Available from most department stores.

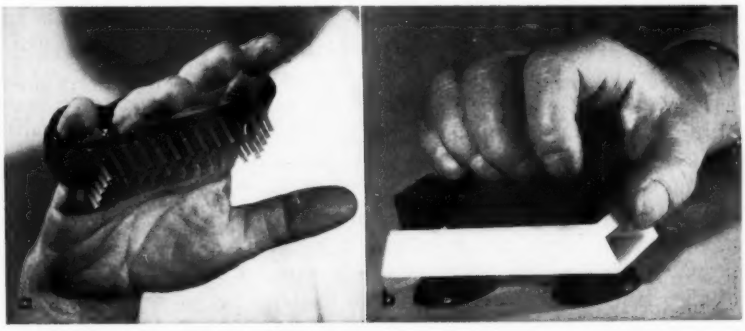

FIGURE 6. An ingenious and practical home-devised soap bag to be worn about the neck can be made from a piece of meshed dishcloth for a few cents.

Readers are invited to submit suggestions and ideas for devices they have developed or know about and would like to share with others. Forward all such comments and suggestions to: Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

Additional information on self-help devices, aids for disabled persons, homemaking training, and other principles of physical medicine and rehabilitation will be found in the new book, "Arthritis," edited by Dr. Lowman and published by Little, Brown & Company, Boston, Massachusetts.

CLINICAL STUDY

Intra-articular Steroid Therapy

COMPARATIVE EFFICIENCY OF 6-METHYLPREDNISOLONE ACETATE IN CASES OF RHEUMATOID ARTHRITIS

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A study was made of the effectiveness of intra-articular administration of 6-methylprednisolone acetate, hydrocortisone tertiary-butylacetate and prednisolone tertiary-butylacetate.

The 6-methylprednisolone acetate was more effective than prednisolone tertiary-butylacetate or hydrocortisone tertiary-butylacetate in five cases; it was less effective than these two steroids in three cases, and equally effective in 30 cases.

In almost all instances the three steroids had a pronounced local anti-inflammatory effect on the rheumatoid process, with little difference in the degree of relief produced by each of the steroids.

THE demonstration of the local anti-inflammatory action of the adrenocortical hormones[1] has been an important contribution to medical practice for two principal reasons: (1) It has reduced the need for the systemic administration of steroids in many cases, and (2) it has improved the effectiveness of treatment of many anatomically limited lesions. It is the purpose of this article to review briefly some of the indications for intra-articular steroid therapy, and to evaluate the effects of a new hormonal preparation, 6-methylprednisolone acetate (MEDROL®), which may be used for this purpose. The literature contains excellent articles[2,3] which describe the technic for injecting steroids into joints and soft tissues.

Hydrocortisone tertiary-butylacetate previously has been the most desirable steroid for intra-articular administration, since this relatively insoluble ester usually produces a local anti-inflammatory effect which lasts longer than that produced by hydrocortisone acetate.[4-6] Prednisolone acetate has no advantage over hydrocortisone acetate. Prednisolone tertiary-butylacetate ($\triangle'$ FTBA), however, is su-

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perior to prednisolone acetate. Its effect lasts as long as that of hydrocortisone tertiary-butylacetate (FTBA), but it appears to produce transient local reactions slightly more frequently than does hydrocortisone tertiary-butylacetate.[7]

Traumatic Arthritis

Traumatic lesions might represent conditions in which the local use of steroid therapy will produce optimal results.[8] If the injury has not caused a fracture or significant damage of soft tissues, intra-articular administration of steroids can be used to suppress the painful irritative reaction and thus avoid disability during the week or so required for normal healing. It is important, however, not to overlook the presence of serious damage of a joint. If such damage is overlooked, the intra-articular administration of steroids may mask the symptoms and thus contribute to the injury of the joint by permitting early use of unhealed or mechanically unstable structures. A single injection of 1 or 2 cc. of a suspension of steroid usually is sufficient in most cases of uncomplicated traumatic arthritis.

Osteoarthritis

The intra-articular administration of steroids is particularly useful when a painful exacerbation occurs in a case of degenerative arthritis in which the disease otherwise is of a low grade. The obese patient with chronic pain in the knee usually will obtain little benefit from this type of therapy. In fact, if too much attention is directed to the intra-articular administration of steroids, it may prevent proper attention from being given to other important therapeutic measures such as reduction of weight, decrease in weight-bearing activities, and correction of flexion contractures, and it thus may lead to aggravation of the articular damage.[8] However, intra-articular steroid therapy may be of great value in tiding the patient over an acute or subacute exacerbation and as an aid to physical therapy in the correction of an early flexion contracture.

In cases of osteoarthritis of the hip, the results of intrasynovial administration of steroids are quite unpredictable. This type of therapy usually does not produce any relief or it produces partial relief which may last for two or three days. In perhaps 20 to 25 per cent of cases, however, it produces a significant reduction in the pain which lasts for a month or more, and this result justifies a trial injection of a steroid.

Heberden's nodes of the finger joints rarely are painful enough to require intra-articular steroid therapy, but this type of treatment is adaptable to some situations.

Rheumatoid Arthritis

The value of intra-articular steroid therapy in rheumatoid arthritis is subject to serious limitations in that the disease process is a systemic one with polyarticular involvement in most cases. However, many patients can be benefited by the judicious use of locally administered steroids. The patient with one knee as the predominantly affected joint often can be kept working and relatively free of pain with an injection every month or two. The patient with a joint contracture that does not respond to physical therapy often can have such a contracture more rapidly corrected with the aid of joint injections. And, most important, some patients need not receive systemically administered steroids, or their oral dosage can be reduced greatly by the periodic local use of small doses of the cortisones.

Material and Method of Study

This study was made to compare the effectiveness of the intra-articular administration of 6-methylprednisolone acetate, hydrocortisone tertiary-butylacetate and prednisolone tertiary-butylacetate. When 6-methylprednisolone and prednisolone are administered systemically in comparable doses, 6-methylprednisolone is about 25 per cent more potent than prednisolone.[9] A suspension of 6-methylprednisolone acetate* was injected into the joints on 122 occasions in 38 cases of rheumatoid arthritis. A suspension of hydrocortisone tertiary-butylacetate or a suspension of prednisolone terti-

*The suspension of 6-methylprednisolone acetate used in this study was supplied by the Upjohn Company, Kalamazoo, Michigan.

ary-butylacetate* was also injected into the joints in these cases. Previous experience indicated that the effects produced by the intra-articular injection of 1 cc. of a suspension of hydrocortisone tertiary-butylacetate (25 mg. of hydrocortisone tertiary-butylacetate) and 1 cc. of a suspension of prednisolone tertiary-butylacetate (20 mg. of prednisolone tertiary-butylacetate) were about equal.

The suspension of 6-methylprednisolone acetate that we used in this study contained 40 mg. of 6-methylprednisolone acetate per cubic centimeter, and the usual dose was 1 cc. The effect produced by this dose was compared with the effects produced by 2 cc. of a suspension of prednisolone tertiary-butylacetate (40 mg. of prednisolone tertiary-butylacetate) and 2 cc. of a suspension of hydrocortisone tertiary-butylacetate (50 mg. of hydrocortisone tertiary-butylacetate).

In addition, 2 cc. of the suspension of 6-methylprednisolone acetate (80 mg. of 6-methylprednisolone acetate), 4 cc. of suspension of prednisolone tertiary-butylacetate (80 mg. of prednisolone tertiary-butylacetate) and 4 cc. of suspension of hydrocortisone tertiary-butylacetate (100 mg. of hydrocortisone tertiary-butylacetate) were administered in 19 of the 38 cases.

Results

The relative effectiveness of these three steroids was as follows. The 6-methylprednisolone acetate was more effective than prednisolone tertiary-butylacetate or hydrocortisone tertiary-butylacetate in five cases; it was less effective than these two steroids in three cases, and it was equally as effective as these two steroids in 30 cases.

In almost all instances in which these three steroids were injected, they had a pronounced local anti-inflammatory effect on the rheumatoid process, and little difference could be detected in the degree of relief produced by each of these steroids. The major consideration was the duration of the local effect. In this respect, 6-methylprednisolone acetate did not differ significantly from prednisolone tertiary-butylacetate and hydrocortisone tertiary-butylacetate. The average duration of the relief that is produced by administering 40 mg. of 6-methylprednisolone acetate, 40 mg. of prednisolone tertiary-butylacetate or 50 mg. of hydrocortisone tertiary-butylacetate was one month. Although larger doses of steroids usually do not increase the degree or duration of the benefit,[10] the duration of the relief was prolonged for one to four additional weeks in six of the 19 cases in which 80 mg. of 6-methylprednisolone acetate was administered.

In five instances, the intra-articular injection of the suspension of 6-methylprednisolone acetate was followed by an aggravation of the articular symptoms which lasted for 4 to 24 hours before the beneficial effect became apparent. This reaction occurred in only one instance in which the steroid was injected into the knee joint. A similar reaction has been observed after the injection of prednisolone tertiary-butylacetate. It presumably is due to injury caused by the injection, but it may be due to the vehicle containing the steroid.

*The suspension of prednisolone tertiary-butylacetate was supplied by Merck Sharp & Dohme, West Point, Pennsylvania.

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CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Gillesby, M.D., Assistant Chief, Surgical Service

Case Report

A 70 year old Negro janitor was admitted to the Hines Veterans Administration Hospital on November 30, 1957, with a three week history of fever and chills following the onset of a cold. The symptoms had subsided four days before admission, and the patient felt fine for one day. The "cold" symptoms returned the next day and were present on admission. The patient complained of a sporadic cough, productive of one-quarter cup daily of a thick, odorless, greenish-yellow sputum. Recently, he had expectorated blood in the sputum. He also stated that for about four days before admission he had pain in the right upper lumbar area, with radiation around the right side to the right upper quadrant of the abdomen. The pain worsened on deep inspiration and coughing. He said that he had not lost any weight recently, and that there had been no contact with anyone with tuberculosis or upper respiratory infection.

For the past few years, the patient had noticed some night sweats. During the past year shortness of breath had been associated with effort and relieved by rest. He had no anginal symptoms. During the week before admission, he noticed that his urine was much darker than usual; he also complained of nocturia four to five times per night. He had recently become constipated, although there was no change in the stool and no melena. He had no itching and had not noticed any icterus in his sclerae. For many years he had had arthritis, involving mostly the peripheral joints. He said he smoked a pack of cigarettes daily and consumed three to four bottles of beer and three to four shots of whisky weekly. On two occasions he had "passed out" following attacks of dizziness.

Physical examination on admission—Temperature was 99.2°F., pulse 88 and irregular, respiration 24 and blood pressure 140/72. The patient was in no acute distress but was breathing slightly laboriously. Only positive findings are described. Funduscopic examination revealed moderate tortuosity of all retinal arterial vessels. The chest was emphysematous, bilaterally symmetrical, with increase in anteroposterior diameter. Breath sounds were normal throughout except for some diminution in the right lower lobe. Dry crepitant rales were heard over the right lower lobe posteriorly. No decrease was noted in tactile fremitus and no abnormalities were found on percussion. The heart rate was 108, with the presence of many drop beats which were spaced at approximate intervals of one every five beats. A_2 equaled P_2. A grade 2 precordial systolic murmur was heard, with no radiation. No thrills were noted. There was slight cardiac enlargement to the left. The liver was 1 cm. below the right costovertebral angle. The spleen and kidneys were not palpable. There was no costovertebral angle tenderness. The prostate was normal in size and normally firm. Bilateral femoral pulsations were noted. There was a moderate amount of tenderness of the right upper flank under the

lateral aspect of the right rib cage when the patient took a deep breath. The pain was nonradiating.

Hospital course—The complaints of chest pain, chills and fever led to an admitting diagnosis of bronchopneumonia and pleuritis involving the right lung and associated arteriosclerotic heart disease. The patient was placed on medical management which included a low sodium diet and the administration of penicillin, ammonium chloride, aspirin, chloral hydrate, phenobarbital and codeine. In addition the patient was given digitalis. For the first few days in the hospital, his temperature remained around 100°F. It returned to normal December 3 and remained there until he died. His pulse and respirations stayed constant at normal levels except on December 4 when they rose to 110 and 24, respectively, over a 12 hour period. By that day his sputum had changed from greenish-yellow to colorless and was then thin in consistency. Also the sinus rhythm had reverted to normal. On December 5 his chest was clear except for occasional fine rales over the left lower lung field posteriorly. He was having very little pain over the right lower rib cage on inspiration. During the next few days he progressed well. He stopped expectorating, and his chest was entirely clear to auscultation and percussion. By December 11 he had become ambulatory and relatively asymptomatic. It was anticipated that he would be discharged within a few days. At 5:40 A.M. on December 12 he suddenly ceased breathing during sleep and was pronounced dead.

Laboratory Studies

Roentgenographic examinations—On November 30 posteroanterior and right lateral views of the chest showed linear areas of increased density involving the lower left field of the lung. A lateral film showed that the densities involved the lower lobe. The aorta was elongated and tortuous. The findings suggested a pneumonic process but were not characteristic of lobar pneumonia; they also suggested platelike atelectasis due to an elevated diaphragm. A posteroanterior view of the chest made December 11 and compared with a film made December 3 showed clearing of the diffuse infiltrates at both of the bases.

Laboratory tests—On November 30 the urine was clear, amber-colored and acid, with no albumin or sugar. Specific gravity was 1.020. Microscopic examination showed occasional white blood cells, no red blood cells, and occasional epithelial cells.

Blood studies: Hemoglobin 15 gm., polymorphonuclear cells 64, lymphocytes 36, sedimentation rate 20, hematocrit 50, blood urea nitrogen 12.3 mg. per cent, creatinine 1.2 and glucose 79.

On December 1 serologic tests gave negative results; hemoglobin 14 gm., white blood cells 6200, hematocrit 51, two hour Watson 0.24 unit per 60 cc. Sputum culture showed alpha and beta hemolytic streptococci and *Neisseria catarrhalis*, but no pathogenic yeasts or fungi.

On December 3 the Van den Bergh reading was 0.24 direct and 0.9 indirect; thymol turbidity 1, alkaline phosphatase 3.1, total protein 6.8 with albumin-globulin ratio of 3.7 to 3.2, total cholesterol 271 with esters 211.

Sputum examination on December 6 showed no acid-fast bacilli on either smear or culture.

Miscellaneous examinations—On December 4 the 1:1000 skin tests for histoplasmosis, blastomycosis and coccidioidomycosis all had negative results. The purified protein derivative test No. 1 was also negative.

On December 2 an electrocardiogram showed the T wave to be low in leads I and II and in V_4, V_5 and V_6. There was sinus tachycardia, and occasional premature auricular and nodal contractions. The T wave changes might have represented a digitalis effect or coronary arteriosclerosis.

On December 5, the electrocardiographic tracing again was abnormal. It was compatible with coronary insufficiency and possibly early left ventricular strain.

DR. EDWARD O. WILLOUGHBY (assistant chief, medical service): A patient such as this 70 year old man might have all or many of the diseases of youth, in either acute or chronic form, and also the diseases of age. The fact of his being a Negro raises a question of sickle cell states. His work, that of a janitor, suggests certain environmental problems, such as work-

ing in a dusty, dirty environment and coming into contact with some dusty, dirty people, rats, or broken fluorescent tubes. As the history showed, the patient was well until three weeks before admission, when he had fever, chills, and an upper respiratory infection. His condition actually improved before he came in and also during his entire hospital stay. The symptoms already described, of course, suggested involvement of the upper and lower portions of the respiratory tract, as well as the organs in the right upper quadrant of the abdomen and the area of the right flank. As the pain mentioned was worse on deep inspiration and coughing, it might properly be called a pleural type of pain, and undoubtedly the diaphragm was involved. Apparently the shortness of breath he had had for about a year was not severe enough to cause him to consult a physician. I cannot say whether the darkness of the urine was the description of an enthusiastic historian or whether the patient noticed it. Later, we find that the urine was normal, with a specific gravity of 1.020, and this does not seem to relate to a urinary infection. The kidneys seemed to be in pretty good condition, and the cause of the dark urine is at present obscure.

The positive findings have been described, and I will assume that the examining physicians carefully checked the lower extremities for any evidence of edema and thrombophlebitis, as well as arthritis. Nothing has been said of any friction rub of the lungs or in the heart. There was a precordial systolic murmur and slight cardiac enlargement to the left. The right upper flank tenderness was noted on deep breathing, but it did not appear to involve the liver. With complaints of chest pain, chills and fever, it was reasonable to consider bronchopneumonia and arteriosclerotic heart disease, and the patient was treated in the usual manner for these ailments. However, I think previous experience would cause all of us to think of thrombo-embolism.

The patient did well, his temperature became normal, and he continued to improve. One day his pulse went to 110 and his respirations to 24. The premature beats—at least the dropped beats—disappeared, and the sinus rhythm was normal. About six days after he was admitted, rales were noted in the opposite lung. The pain in the right lower rib cage decreased, there were no further physical findings, no more sputum, and by the eleventh he was up and about. But on the twelfth he suddenly died in his sleep.

Neither the urinalysis nor the blood studies provided any clues. The two hour Watson reading was 0.24 unit per 60 cc., while the normal is from 1 to 1.25 units per two hours. It is rare to find an abnormal urobilinogen unless the specimen is sent to the laboratory immediately, because standing apparently will cause the pigment to be metabolized and give uniformly low levels. However, this fits with the protocol and is normal. Both of the electrocardiographic reports are suspicious in view of the whole picture. The T wave is low in leads I and II and in V_4, V_5 and V_6, and there were occasional premature auricular and nodal contractions. This may represent digitalis effect or coronary arteriosclerosis. The tracing made three days later was abnormal and compatible with coronary insufficiency and possible early left ventricular strain.

DR. WILLIAM FREDERICK (assistant chief, radiology service): A chest film dated November 30, 1957, showed a diffuse, irregular density of both bases, which was irregular and somewhat more advanced on the right. The upper lung fields were essentially clear. The heart measured about 17 cm. The enlargement was diffuse and appeared to involve no special chamber. The aorta was tortuous. There was no calcium in the ascending segment, but there was calcium in the arch and the descending branch of the thoracic aorta.

In a film dated December 6, the heart measured 14.5 cm., a decrease of almost 3 cm. The density adjacent to the right side of the heart was more evident than on the earlier film. On the left side there was clearing, but some density. The remaining lung fields were clear.

Three days later, on a film dated December 9, there was further resolution of the findings at the right base. The left side was clear. There was a radiolucent area adjacent to the right heart border between the density described and the heart.

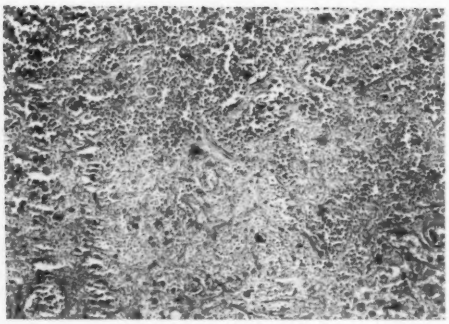

FIGURE 1. Infarction of lung.

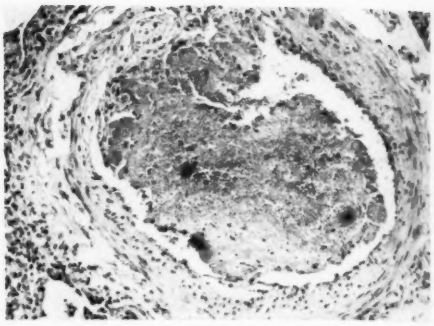

FIGURE 2. Embolus in pulmonary artery.

The next film made two days later showed the heart to measure about 15 cm. The configuration was fairly normal. The density at the right base was still present. The upper lung fields were clear. The calcium in the aortic walls was again well demonstrated.

Impression: The findings began as a reactive inflammatory process in the lung fields with an enlarged heart. The findings diminished in the lungs and the heart became smaller. These findings suggest (1) pulmonary infarcts at both bases with resolution; (2) generalized cardiac enlargement which apparently responded to medication, and (3) advanced arteriosclerosis.

DR. WILLOUGHBY: You feel that the density in the right lower was pneumonitis or infarct?

DR. FREDERICK: I think it was pneumonitis as the result of infarct.

DR. WILLOUGHBY: I do not believe that we can avoid making the intermediate diagnosis of thrombo-embolic phenomena involving the lungs. That may be an error, but in any case I have not pinpointed the site of the thrombosis if it was outside the thoracic cage. Where do people get thromboses that go to the lungs and cause pulmonary infarcts? Obviously thromboses may occur any place in the right side of the circulatory system, in the peripheral veins up to and including the right atrium, in the right ventricle and extending to the pulmonary artery, or in the lung itself in one branch of the pulmonary artery. There is nothing in this history as to peripheral thrombophlebitis. Of course, the man could have had a phlebothrombosis without much pain. Sometimes the first signs of this condition are those of pulmonary embolism. Another cause for thrombophlebitis of the legs is sitting before a television set or sitting in any position.

Any severe effort, which a janitor might make in working around an apartment building, would predispose to that type of thrombophlebitis. A person may have thrombophlebitis in areas which are quite inaccessible to ordinary physical examination, such as within the pelvis. In men, the prostatic bed may be the source of a pulmonary embolism. In a case like this one, involving ventricular fibrillation, the right side of the heart may harbor clots, which may take the shape of ball thrombi. I was intrigued, at least in passing, by the x-rays. I do not believe that this man had any signs of ball thrombus other than the sudden attacks of dizziness and fainting on two occasions. He had no gangrene at the tips of the nose, penis or fingers. There did not seem to be any change in heart murmurs.

With myocardial infarction the left ventricle is usually the more severely involved, although the infarct may extend to involve the right ventricle. It may produce the subendocardial thromboses which may embolize to the lung and produce this syndrome. Thrombosis of the pulmonary artery does occur, often in very small vessels. As the lung is constantly in motion, thrombosis of pulmonary arteries is less common than we would suspect.

As we review the case, we see that there are a great many things that point to a pulmonary embolus thrombosis. Among the signs

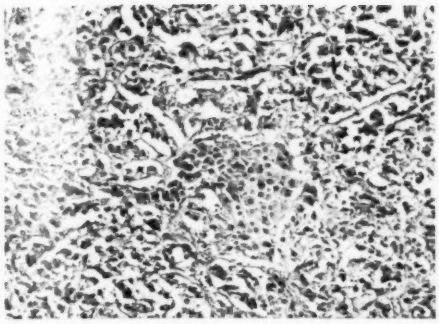

FIGURE 3. Pheochromocytoma around island of adrenocortical tissue.

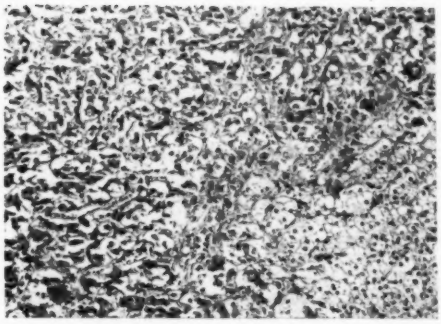

FIGURE 4. Pheochromocytoma extending into adjacent adrenal cortex.

that do not indicate it are the dark urine and the nocturia, which might have been secondary to some cardiovascular insufficiency. The exertional dyspnea was consistent with the congestive heart-failure; the chills may have been secondary to an infected pulmonary infarct. The greenish-yellow sputum may also have been caused by the infected embolus.

In closing, I shall mention the more or less fancy association of thrombo-embolic disease with carcinoma. That was described by Trousseau in 1865, and it has been gradually rediscovered. It is fashionable to say that the cause of obscure thrombophlebitis is commonly carcinoma of the lung or gastrointestinal tract, especially of the pancreas. Some mention was made of difficulty with the right upper quadrant of the abdomen. I do not say that there was any neoplasm in the kidney. There was no evidence of that. I do not believe the symptoms were those of carcinoma of the pancreas. Some people doubt that there is a bona fide association of thrombo-embolic disease with intra-abdominal or intrathoracic carcinoma. This has not been entirely worked out, but I have noted references which show that it is rather futile to make a fantastically involved excursion into the diagnosis of carcinoma when a previously well patient has a thrombophlebitis. Certainly a chest x-ray should be taken and stools should be checked for blood. Carcinoma of the pancreas seldom shows up on a gastrointestinal series.

DR. ROBERT FRUIN (section chief, gastroenterology): I think the thrombo-embolic phenomena is the most likely diagnosis. There is another situation that might be mentioned, although there is nothing in the findings to substantiate it. When a 70 year old man with obvious findings of arteriosclerosis has pleuritic pain and suddenly dies, one should think of a leaking aortic aneurysm that ruptures.

DR. WILLOUGHBY: I think this man had a pulmonary embolism at a site I am not able to delineate. I am unable to include or rule out an intra-abdominal carcinoma. I believe that this man had congestive heart-failure which was compensated by treatment.

DR. MYRON E. RUBNITZ (chief, laboratory service): At autopsy there was evidence of recent and older pulmonary infarction (figure 1), although there was no gross evidence of pulmonary embolism. The heart was slightly enlarged with marked coronary arteriosclerosis and a few patchy areas of myocardial fibrosis. There were no thrombi in either of the auricular appendages. The source of the pulmonary embolization, seen microscopically (figure 2), could not be determined at autopsy. With the history of auricular fibrillation, it is highly possible that the emboli came from the right auricular appendage. Sections through the areas of pulmonary infarction showed the typical hemorrhagic appearance, with the characteristic indurated bulging of the parenchyma. On microscopic examination the extensive parenchymal necrosis with hemorrhage corroborated the gross impression. Many of the smaller pulmonary arteries had thrombi in the lumina which appeared to vary

in age, from very recent to older. The intimal layer, as well as other layers of the arterial walls, failed to show any inflammatory, metabolic or degenerative changes, so there is little likelihood of this being a case of primary pulmonary artery thrombosis. The attachment of the emboli to the intimal layer in some of the vessels probably was due to the older age of the blood clot.

An interesting and possibly complicating feature of this case was noted when the adrenal glands were examined. The right adrenal gland was larger than the left, and weighed 15 gm. On cut section the medullary portion was not only demonstrable but was also enlarged and seemingly impinging the surrounding cortex. With microscopic examination, the diagnosis of probable pheochromocytoma was made more tenable. There was a marked proliferation of large polygonal and fusiform cells with abundant clear or granular cytoplasm, some containing pigment granules which gave a positive chromaffin reaction when stained. The nuclei were large and generally uniform in size and shape, some containing nucleoli. In many areas these cells presented in an alveolar pattern, arranged delicately around small vascular structures, particularly capillaries. No evidence of malignancy was found. Small islands of cortical cells often were found surrounded by the pheochromocytes and pheochromoblasts which appeared to be growing into the peripheral layers of the adrenal cortex (figures 3 and 4).

It, therefore, appears that the lesion fits into the category of pheochromocytomas in which no hypertension is ever clinically demonstrated. However, it must be pointed out that very few blood pressure readings were recorded on the patient's record. It is possible that he might have had transient episodes of hypertension which were undetected. The two known attacks of dizziness and unconsciousness could well be explained on the basis of a pheochromocytoma. Sudden death with this type of tumor is not uncommon, and such cases are reported even with no recorded hypertension.

DR. WILLOUGHBY: How large was the pheochromocytoma?

DR. RUBNITZ: It measured about 1 cm. in diameter.

DR. WILLOUGHBY: I understand that there are small benign tumors of the adrenal cortex which are frequently found and which may not clinically reflect an endocrine function. Is that so in cases of the somewhat frequent findings of small adrenocortical adenomas?

DR. RUBNITZ: Most small, apparently encapsulated adrenocortical tumors are not true adenomas, but rather are small foci of cortical hyperplasia with no endocrine dysfunction whatever. True cortical neoplasm, of course, may cause extensive endocrine disturbances. The cortical tumors are generally yellow or brown in contrast to the medullary tumors which are grayish in color.

DR. ARMAND LITTMAN (chief, medical service): I submit the opinion that the pheochromocytoma was an incidental finding. The patient's complaints that Dr. Rubnitz has attributed to pheochromocytoma are of the garden variety. A more positive reason to deny the role of this tumor in the patient's symptoms is that the effect of a secreting pheochromocytoma is usually clear-cut. It is true that some patients have a silent sustained hypertension that resembles ordinary essential hypertension of varying degree and that such patients may indeed have this hypertension on the basis of pheochromocytoma. Most of the patients with pheochromocytoma that one sees do indeed have the more typical manifestations of paroxysmal attacks.

DR. RUBNITZ: I would have to agree that the great majority of these lesions are associated with some functioning and circulating material which would cause hypertension, which this man apparently did not have, at least as far as we know. I can only put this down as a possibility and as a good possibility for his death. We have seen many patients who have died suddenly as the result of pulmonary emboli. There is usually a well-demonstrated embolus blocking one of the major pulmonary arterial radicles. This was not seen.

DR. MARIAN TARZYNSKI (resident, gastroenterology section): Was the brain examined?

DR. RUBNITZ: Nothing was found on gross or microscopic examination of the brain.

Editorials

Postgraduate Medicine

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TONICS

Fifty years ago, a favorite prescription of many physicians was iron, quinine and strychnine given as a tonic. Apparently it must have served some purpose—perhaps largely psychosomatic—but in any event, the tonic prescription seems to have largely disappeared. It has been replaced by prescriptions principally of iron for secondary anemias and by vitamins in general. As Dr. J. C. Houston,[1] Guy's Hospital, London, said, "Fashions change in drugs as in diseases, and it cannot be denied that tonics have acquired a distinctly old-fashioned flavor." Nowadays, the wish is apparently not for drugs that will stimulate but for drugs that will tranquilize and relax.

In the old days, glycerophosphates were frequently prescribed with the idea that in some manner they would help the nerves. The nerves were recognized to contain considerable amounts of phosphorus. When it was discovered that the lecithin in the central nervous system contains phosphorus, the glycerophosphates began to be used, principally in such patent medicines as Sanatogen. Evidence was not available, however, to indicate that glycerophosphates taken orally exerted any pharmacologic or metabolic effect whatever. Nevertheless, they still form a part of many proprietary tonics.

Once upon a time, strychnine, usually in the form of tincture of nux vomica, was the most frequently prescribed of all drugs in the pharmacopeia. Modern pharmacologists teach that the only value of strychnine in therapeutic doses is its action as a bitter; gentian is probably just as good, and at the same time, it is cheap and harmless.

Alcohol was used in the past and still is used as a tonic. Here is not the time or place to discuss its benefits or faults. Perhaps the most that can be said for alcohol is that under certain circumstances it may create a feeling of euphoria, which is extremely useful.

When amphetamine became available, it was used for increasing mental activity and for making the patient feel more energetic and cheerful. It was the drug primarily used for overcoming depression. Nowadays, at least a half-dozen psychic energizers are available and will undoubtedly replace amphetamine for

the purposes indicated, principally because at least some of the psychic energizers do not seriously raise the blood pressure. Moreover, side effects such as dryness of the mouth, headache, insomnia, and loss of appetite seriously contraindicate using amphetamine as a psychic energizer.

Dr. Houston mentioned the combination of a tranquilizer with amphetamine. Such combinations as meprobamate with an energizer like benactyzine already are being used extensively by the medical profession.

When all these considerations have been properly evaluated, one must come to about the same conclusions that were reached by Dr. Houston. Vitamins when indicated for specific deficiencies are important in medicine, but they are not tonics. When the diet is inadequate or restricted, vitamins are certainly necessary. When they are not properly absorbed, when antibiotic therapy interferes with their use, or when the metabolic requirements are increased, vitamins should be prescribed. However, with drugs that increase mental activity or with drugs used to overcome fatigue, one should remember that the old proverb that indicates it is wrong to whip a tired horse still prevails. Said Dr. Houston, "Tonics may be helpful in making a patient feel temporarily better, but they cannot restore vitality destroyed by chronic anxiety and overwork or take the place of adequate convalescence after serious illness. They should not be a vehicle for specific remedies used indiscriminately and are usually none the worse for being simple and inexpensive."

MORRIS FISHBEIN

REFERENCE

1. Houston, J. C.: Tonics. Brit. M. J. 1:1236-1237 (May 9) 1959.

A VISIT TO THE MOON

In the *British Medical Journal*, Drs. A. S. Parkes and Audrey U. Smith[1] of the National Institute for Medical Research in Great Britain published a paper which they delivered to the British Interplanetary Society in September 1958. The announcement of the successful planting of a rocket on the moon by the Russians gives added interest to this report.

On the moon there is no atmosphere, little (if any) water, and wide and sudden swings of temperature. Any talk of sending human beings to the moon must recognize these facts about the living conditions. Interplanetarians have already collected similar climatologic information about Mars, Venus, Mercury and even Jupiter, Saturn and Neptune. In addition to the hazards which will greet the visitor on arrival are these recognized exposures to which he will be submitted en route: cosmic rays, especially those trapped immediately above the earth's atmosphere; hard x-rays given out by the sun; and intense ultraviolet irradiation. Moreover, tremendous extremes of temperature will be encountered. Obviously, some planning will be required to overcome these influences. The biologists who have been called in counsel already have begun to attempt to work out some ways by which life could be maintained in human beings, allowing them to arrive on some of these far-distant places in reasonably good condition.

Freezing and drying technics have already been found which will maintain life in lower animals on a lower level without permanent damage to the system. Many lower organisms and most plants produce spores or seeds which have a low water content and a negligible respiration rate and thus have a high resistance to cooling, drying and lack of oxygen. Bacteria and protozoa from frozen soil obtained in Siberia when carcasses of mammoths frozen for at least 50,000 years were unearthed have been grown in cultures. Well-authenticated examples are available of seeds of higher plants which have remained viable for hundreds or even thousands of years. This permits the theory that modern technics of freeze-drying might be applied to human beings in order to enable their transportation under proper circumstances to the moon or other far-removed places.

Newspaper accounts say that the Russians carefully sterilized the rocket inside and out before sending it to the moon for fear of transporting pathogenic organisms. If people ever go to the moon, quite certainly they will take

along as fellow travelers their permanent residential bacteria. The biologists consider it quite unlikely that animal life in the sense of self-propagating matter ultimately dependent on plant food has evolved at all on any of the planets. If so, the lines of development might be quite different from any of those known on earth. Any life based on biochemical reactions, say the British biologists, will be rather sluggish, particularly on the outer planets, and they doubt that evolution could have proceeded to living beings who are anything like those on earth.

Vertebrate animals, even cold-blooded ones, do not tolerate extensive freezing. Vertebrates cannot survive conversion of their body water to ice. Revival of fish and frogs found frozen solid in blocks of ice depends on the lower freezing points of their blood and tissue fluids. Hibernating animals can survive reduction of body temperature to a few degrees above 0° C. without damage. Experiments have been made on bats. By special methods, mice, rats, dogs and monkeys have been revived from body temperatures approaching 0° C. after cessation of breathing and heartbeats for up to one hour. The best results have been achieved with the hamster, a potential hibernator. With this animal the experiment has been pushed further, and body temperature has been reduced to below zero by immersing the hamster in a bath at –5° C. Hamsters have been resuscitated undamaged after being below the freezing point for one hour, at which point some 50 per cent of their body water had been converted to ice.

Some Russian biologists have suggested that bats and other mammals might be supercooled to lower temperatures and so kept in a comparatively stable state. The British biologists therefore suggest that the first space explorers might take bats in the spaceship. They conclude that the biologist is not within sight of obtaining long-term suspended animation in warm-blooded animals or any other vertebrate, but that it would be a mistake to suppose that this never will succeed.

For surgical procedures in human beings, temperatures have been reduced to 28° C. without destructive effects. The heart still beats slowly and natural breathing can, if necessary, be supplemented by artificial respiration. This should not be called deep-freeze. New technics such as the injection of potassium ions into the coronary circulation and maintenance of a systemic circulation of oxygenated blood by an artificial heart-lung machine are obviously of special interest in connection with maintenance of life under adverse conditions. A recent report described a patient cooled to a deep body temperature of 9° C. without circulation of the blood through the pump. The heart was at a standstill for one hour. After rewarming, this patient recovered consciousness and survived 38 weeks without any apparent alteration in neurologic or intellectual function.

The final conclusion of Drs. Parkes and Smith is that "science fiction notwithstanding, the prospect of suspending animation for indefinite periods in man by freezing him is remote." Freezing would create immunity from the effects of violent acceleration or deceleration. It would diminish the effects of irradiation. It would lessen the need for oxygen. Suspended animation would avoid the effects of old age which might develop in people on long journeys of, let us say, millions of miles. Another tricky problem would be finding a way to dispose of dead people while en route. This leads to the ultimate decision that the first problems of space travel lie with the physicist, the engineer and the medical physiologist. The whole story is fascinating, but perhaps for the present generation of human beings it may be of little immediate value.

MORRIS FISHBEIN

REFERENCE

1. Parkes, A. S. and Smith, A. U.: Transport of life in the frozen or dried state. Brit. M. J. 1:1295-1297 (May 16) 1959.

ENDURANCE CONTESTS AND MARATHONS

In June 1957 a radio marathon was held in which two broadcasters (so-called disk jockeys) competed for the title and a $500 prize.[1] Both men remained awake for 168 hours and 33

minutes, at which time the contest was terminated by the attending physician. The participants alternated every 30 minutes at the microphone. From the fourth day on, they received 5 mg. of dextro-amphetamine twice a day. Both drank much coffee and when not at the microphone stayed awake by walking, smoking and conversing with friends. Abnormal symptoms were noted in both from the fourth day onward. During the last two days both contestants became increasingly delusional and showed disorganization of consciousness. They had auditory and visual hallucinations; the broadcast material was confused and rambling. The physician brought the contest to an end because the behavior of both contestants was increasingly psychotic and because both contestants had swelling of the ankles in addition to tremors.

Immediately following the contest, one contestant ran out the door and was found four hours later wandering around without any memory of what had happened. Eventually, one patient was placed in a Veterans Administration Hospital, where he remained four months, receiving occupational, recreational and group therapy and also, twice a week, some psychotherapy. This man's record revealed that he had been discharged from the army in 1945 for physical reasons, with anxiety states and emotional instability. He had been hospitalized three times for nervous disorders. In November 1956, during a period of prolonged sleep deprivation, this man experienced dissociative symptoms. In March 1957 he tried a radio marathon alone, during which he remained without sleep for 89 hours, and his mental state became progressively confused. After he recovered he had memory lapses lasting 20 to 30 minutes. Yet, with this sort of record concerning his mental state, he was permitted to indulge in another such performance in June 1957.

Depriving people of sleep has been used in so-called brainwashing technics to elicit false confessions. The method has apparently been used in police states as a special form of punishment. Obviously, compulsory deprivation of sleep is sadistic and inhuman. The testing of the human body as to its maximal endurance in such weird contests as radio and dance marathons, pie-eating contests, and bouts of drinking is without the slightest warrant as a source of amusement. Physicians who happen to be associated with such contests will do well to make certain of both the physical and mental health of the participants before lending their prestige to the performance.

MORRIS FISHBEIN

REFERENCE

1. Brauchi, J. T. and West, L. J.: Sleep deprivation. J.A.M.A. 171:11-14 (September 5) 1959.

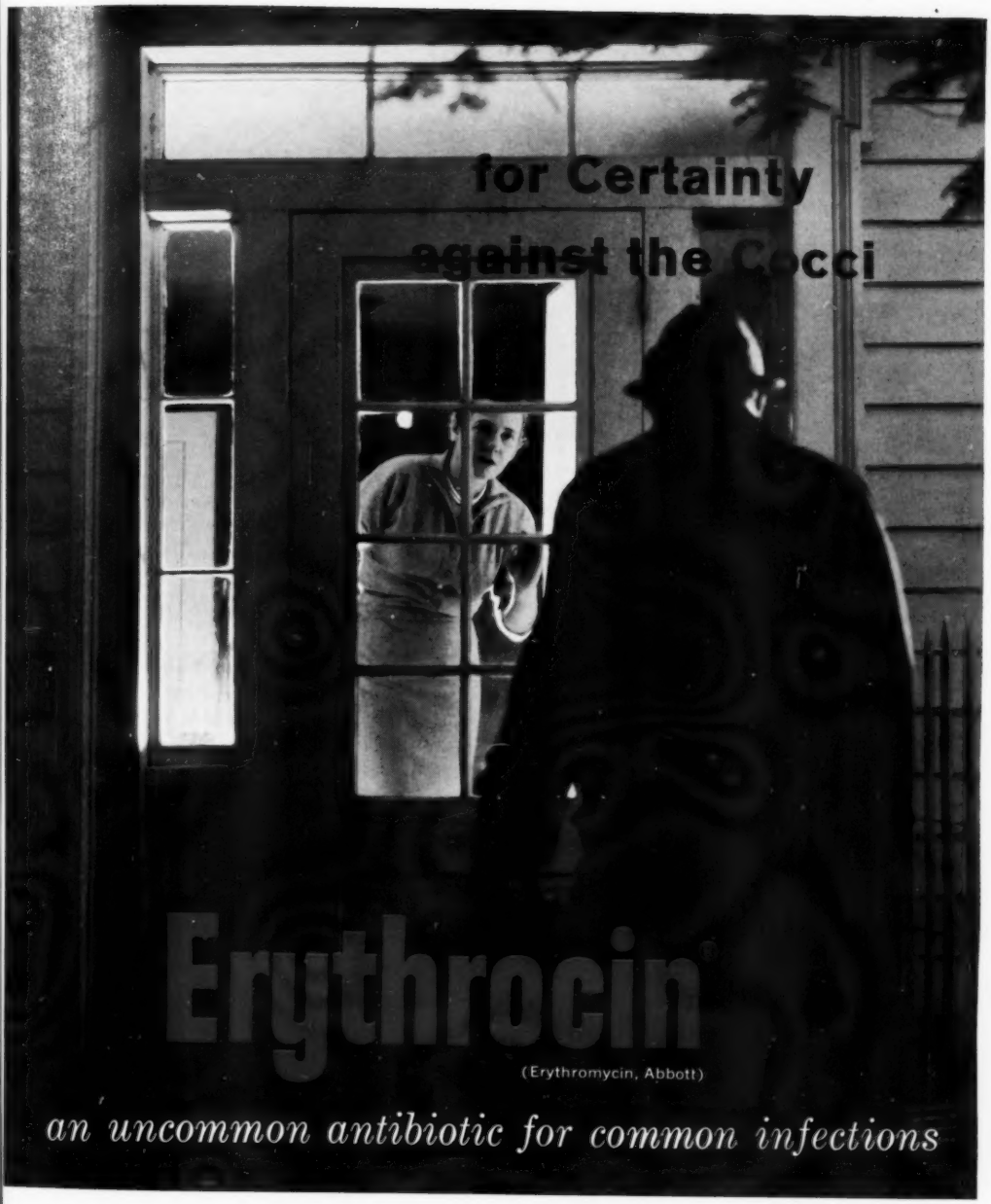
THE RESULTS OF REHABILITATION

The report of the Office of Vocational Rehabilitation, directed by Mary E. Switzer, shows that 80,720 persons were rehabilitated during the year ending June 30, 1959. This figure is a new high for this service. Economists estimate that these people will increase their annual earnings during their first year of employment from about $25 million to $156 million. Rehabilitation costs relatively little compared with the amount of financial gain. Some 16,000 of those rehabilitated have been on relief at an annual cost of about $15 million; the rehabilitation cost $14 million.

Among those rehabilitated, 4000 went into professions, including teaching, engineering and medicine; over 9000 went into trades for skilled workers, and 7000 went into agriculture. The remainder entered such positions as were available for unskilled labor, and some became clerks, members of sales forces, and semiskilled workers.

Many states are still not taking advantage of the knowledge of rehabilitation and the financial support that is now available. Pennsylvania leads all other states in the number of persons rehabilitated, with 6,117; Georgia is second with 5,682, and New York is third with 5,504. This represents a social advance in which the medical profession has cooperated completely and in which the cooperation of medicine and government indicates how much can be done when suitable programs are found for cooperative effort.

MORRIS FISHBEIN



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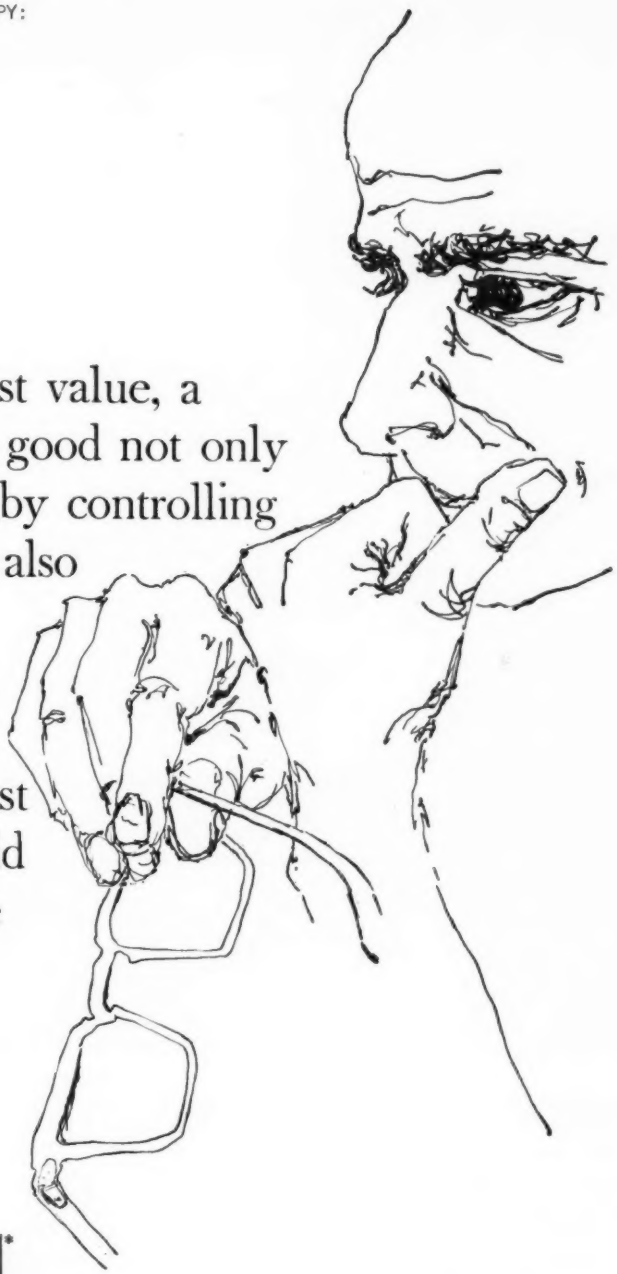
COMPOSITION: Clemizole hydrochloride.
CAUTION: Drowsiness may occur.
DOSAGE AND ADMINISTRATION: Usual adult dosage is 2 to 4 tablets daily in divided doses. Up to 8 tablets a day may be taken if circumstances warrant. Usual dosage for three to six year old children is ½ to 2 tablets daily; for children more than six years old, 1 to 3 tablets daily.
HOW SUPPLIED: 20 mg. tablets in bottles of 100.
PRODUCER: J. B. Roerig and Company, division of Chas. Pfizer & Co., Inc., New York.

• PANHEPRIN® 40,000

PURPOSE: Management of atherosclerosis and hyperlipemia.
COMPOSITION: Heparin sodium solution (40,000 U.S.P. units per milliliter).
CAUTION: Precautions should be taken against hemorrhage; if it occurs, it should be treated actively.
DOSAGE AND ADMINISTRATION: 40,000 units administered intramuscularly or subcutaneously. Since a single injection may diminish hyperlipemia for several days, the drug may be given only two or three times a week.
HOW SUPPLIED: 2 ml. vials in boxes of five.
PRODUCER: Abbott Laboratories, North Chicago.

(Continued on page A-158)

REFLECTION ON CORTICOTHERAPY:



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PRODUCER: Abbott Laboratories, North Chicago.

• PHENOXENE

PURPOSE: Symptomatic treatment of Parkinson's disease.

COMPOSITION: Each tablet contains 50 mg. chlorphenoxamine (beta-dimethylaminoethyl [p-chloralpha-methyl-benzhydryl] ether hydrochloride).

CAUTION: Minor side effects typical of most antiparkinsonism drugs occasionally occur, but are usually well tolerated.

DOSAGE AND ADMINISTRATION: Usual dose is 1 tablet three times daily.

HOW SUPPLIED: Bottles of 100.

PRODUCER: Pitman-Moore Co., Indianapolis.

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DOSAGE AND ADMINISTRATION: Average adult dose is 2 Trablets at bedtime, or as directed by physician. 1 to 2 Trablets three or four times daily may be required initially.

HOW SUPPLIED: Bottles of 100.

PRODUCER: Ames Company, Inc., Elkhart, Ind.

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PRODUCER: American Optical Company, Instrument Division, Buffalo.

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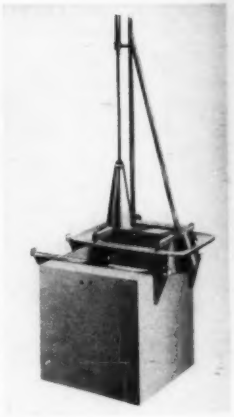

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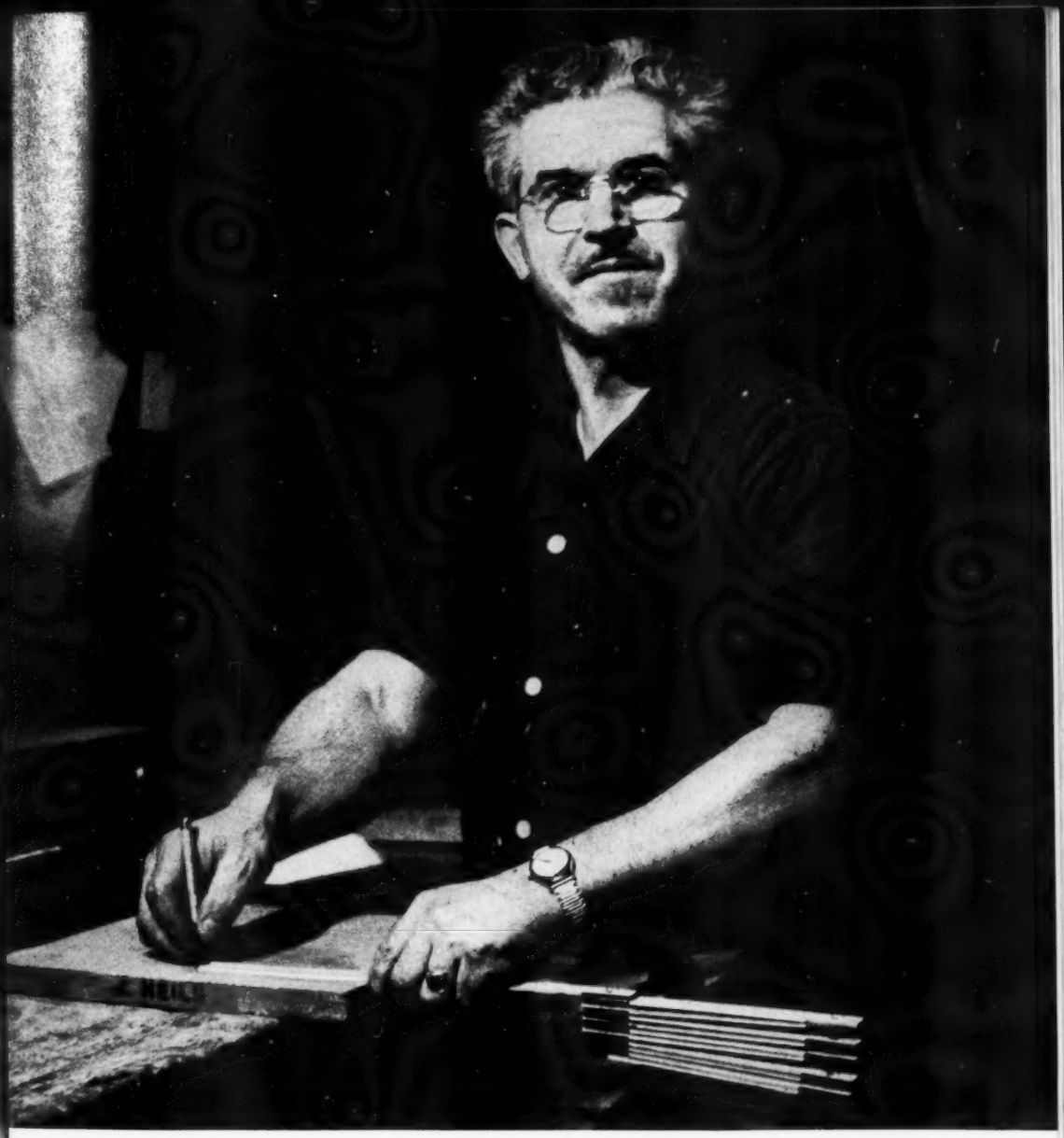
PRODUCER: Victoreen Instrument Company, Cleveland.

(Continued on page A-160)



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PRODUCER: Coleman Instruments Inc., Maywood, Ill.

(Continued on page A-162)

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PRODUCER: American Optical Company, Instrument Division, Buffalo.

(Continued on page A-164)

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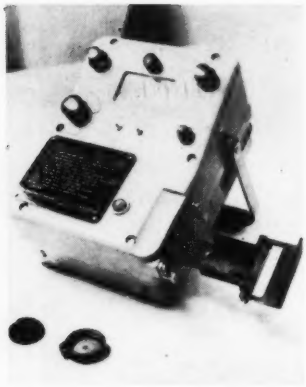


• RADIAC DETECTOR AND COMPUTER-INDICATOR

DESCRIPTION: Designed to be worn as a pendant or carried in a pocket or purse, the phosphate glass x-ray and gamma ray dosimeter records exposure to radiation cumulatively from 10 to 600 r. The sensitive element in the dosimeter emits luminescent light under near ultraviolet irradiation after exposure to x-rays or gamma rays. The portable companion reader operates on five 1½ V, size D flashlight batteries. The unit can handle approximately 200 readings an hour and has two scales (0-200 and 0-600 r), which may be increased by factor up to 100 with a simple modification.
PRODUCER: Specialty Electronics Development Corp., Syosset, N. Y.

• DECADRON® PRODUCTS

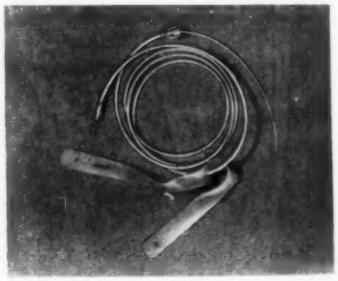
DESCRIPTION: Including topical creams and ophthalmic ointments and solutions, these six topical steroid products are indicated in the treatment of allergic skin disorders and various inflammatory eye conditions, respectively. The same package sizes and dosage forms are available containing dexamethasone 21-phosphate (Decadron Phosphate) alone and in combination with neomycin sulfate (NEODECADRON®). The products are: Decadron Phosphate 0.1% Topical Cream, NeoDecadron 0.1% Topical Cream, Decadron Phosphate 0.1% Ophthalmic Solution, NeoDecadron 0.1% Ophthalmic Solution, Decadron Phosphate 0.05% Ophthalmic Ointment, and NeoDecadron 0.05% Ophthalmic Ointment.
HOW SUPPLIED: Creams in 5 and 15 gm. tubes; solutions in 5 cc. dropper bottles; ointments in 3.5 gm. tubes.
PRODUCER: Merck Sharp & Dohme, division of Merck & Co., Inc., Philadelphia.

• AUTOANALYZER® FLAME PHOTOMETER

DESCRIPTION: Completely automatic, this flame photometer for sodium or potassium analysis, or both, eliminates sample preparation and continuously records results. Diluting error is avoided by means of the continuous flow system. By dialysis, the instrumental system eliminates proteins which clog the burner.
PRODUCER: Technicon Instruments Corporation, Chauncey, N.Y.

• EMERGENCY IDENTIFICATION CARDS

DESCRIPTION: To be carried by persons being treated with anticoagulant drugs, these cards indicate the type of drug being taken, give a prescription for restoration of normal coagulation, and provide space for blood type and weight and the name of the patient's regular physician. The cards are being distributed on request to physicians in pads of 10. Emergency cards also are available for persons with glaucoma.
PRODUCER: Abbott Laboratories, North Chicago.



• PORTEX-GIBBON CATHETER

DESCRIPTION: Lightweight and flexible, this catheter has tubing in sizes 4⅘, 6, 9 and 12 on the Charrière scale, with a wall thickness of 0.25 to 0.5 mm. The catheter is approximately 5 ft. long, with a rounded solid tip and three adjacent side holes for fluid drainage. Two Portex wings provide for comfortable wear. The catheter will not cling to uretheral secretions, and it can be repeatedly autoclaved. A stepped adapter at one end fits onto the inlet of a Lane bottle and onto the nozzle of most bladder syringes.
PRODUCER: R. A. Hawks Division, Sierra Engineering Company, Sierra Madre, Calif.

(Continued on page A-166)

no asthma symptoms—Prophylactic use of Tedral in any of its 5 convenient dosage forms permits most bronchial asthma patients to breathe normally, live actively, avoid social embarrassment. Tedral keeps patients safely free of constriction, congestion and apprehension. When attacks are frequent, prescribe 1 or 2 plain Tedral tablets q.4.h. plus an additional tablet at the first sign of symptomatic breakthrough. Tedral protects up to 4 hours.

Formula: Each scored, plain Tedral tablet contains: Phenobarbital, 8 mg. (⅛ gr.) (Warning: May be habit forming); Theophylline, 130 mg. (2 gr.); Ephedrine, HCl 24 mg. (⅜ gr.)

TEDRAL®

the dependable antiasthmatic

WARNER CHILCOTT

MORRIS PLAINS, N.J.

• SIMILAC® WITH IRON

PURPOSE: Iron-fortified infant formula.
COMPOSITION: Each quart of Similac contains 12 mg. of ferrous iron.
INDICATIONS FOR USE: In cases of placental or traumatic blood loss, unsatisfactory blood picture, prolonged infection or diarrhea, and iron-deficiency anemia; for premature infants and twins; and to support the normal diet.
HOW SUPPLIED: Powder in 1 lb. cans; liquid in 13 fl. oz. cans.
PRODUCER: Ross Laboratories, Columbus, Ohio.

• TIGAN
(New Dosage Form)

DESCRIPTION: Pediatric suppositories containing 200 mg. Tigan hydrochloride.
HOW SUPPLIED: Packages of 6.
PRODUCER: Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, N. J.

• LIQUAEMIN® SODIUM
(New Dosage Form)

DESCRIPTION: This anticoagulant is now available in 5 and 10 cc. vials containing 20,000 U.S.P. units (200 mg.) heparin sodium per cubic centimeter in aqueous solution.
PRODUCER: Organon Inc., Orange, N. J.

• ACTIFED® TABLETS AND SYRUP

PURPOSE: Antihistaminic nasal decongestant and bronchodilator.
COMPOSITION: Each tablet contains 2.5 mg. triprolidine hydrochloride (Actidil) and 60 mg. pseudoephedrine hydrochloride. Each 5 cc. syrup contains 1.25 triprolidine hydrochloride and 30 mg. pseudoephedrine hydrochloride.
DOSAGE AND ADMINISTRATION: The drug is administered three times daily in the following amounts: for adults and older children, 1 tablet or 2 teaspoons syrup; for children four months to six years of age, ½ tablet or 1 teaspoon syrup; for infants up to four months of age, ½ teaspoon syrup.
HOW SUPPLIED: Tablets in bottles of 100; syrup in 1 pt. bottles.
PRODUCER: Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N.Y.

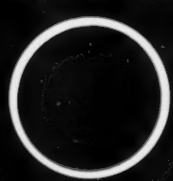
a single injection of
"PREMARIN" INTRAVENOU

increases prothrombin concentration

increases accelerator globulin

and simultaneously depresses antithrombin activity

within 15 to 30 minutes.

Thus, coagulation is enhanced

to achieve prompt hemostasis.

SYNTETRIN – a new synthetic derivative of tetracycline – has these attributes of significant value in therapy:

- effective antibacterial activity is sustained – *even at its lowest blood levels* – throughout therapy
- total antibiotic activity of SYNTETRIN I.M. more than twice that with tetracycline phosphate complex I.M. over a 24-hour period
- highly soluble over the entire physiological pH range (2,500 times more soluble than tetracycline) resulting in more efficient absorption from intramuscular sites than other tetracycline I.M. preparations

An important advantage of SYNTETRIN is that the *lowest* blood levels reached before ensuing daily injections are either maintained or increased. This means that antibiotic levels will not drop below those required to inhibit certain pathogens during the course of therapy. Successive blood level peaks generally rise after repeated injections.

Parenteral **SYNTETRIN** is recommended for initial therapy in infections caused by tetracycline-sensitive organisms in:

1. Patients who require frequent force-feeding or special diets based on milk, which interfere with antibiotic absorption.
2. Patients with diseases causing absorption difficulties.
3. Patients unable to take anything by mouth.

1. Gottstein, W. J.; Minor, W. F., and Cheney, L. C.: J. Am. Chem. Soc. **81**:1198, 1959.

for intramuscular injection

SYNTETRIN I.M.

N–(PYRROLIDINOMETHYL) TETRACYCLINE WITH XYLOCAINE®* FOR INTRAMUSCULAR USE

Supplied in dry-fill single dose vials:

SYNTETRIN I.M. '350' contains:		SYNTETRIN I.M. '150' contains:	
SYNTETRIN	350 mg.	SYNTETRIN	150 mg.
Lidocaine	40 mg.	Lidocaine	40 mg.
Ascorbic Acid	300 mg.	Ascorbic Acid	300 mg.

*Xylocaine is the registered trademark of Astra Pharmaceutical Products, Inc. for lidocaine.

for intravenous infusion

SYNTETRIN I.V.

N–(PYRROLIDINOMETHYL) TETRACYCLINE FOR INTRAVENOUS INFUSION

Supplied in dry-fill vials, each containing: SYNTETRIN ..... 700 mg.
Ascorbic Acid ..... 500 mg.

Detailed information on indications, dosage and precautions is contained in package insert; or, write to Medical Director, Bristol Laboratories Inc., New York, New York.

BRISTOL

THE MEDICAL Bookman

► PANCREATITIS
A Clinical-Pathologic Correlation

By Herman T. Blumenthal, M.D., Associate Professor of Pathology, St. Louis University School of Medicine, and J. G. Probstein, M.D., Associate Professor of Clinical Surgery, Washington University School of Medicine, St. Louis. 379 pages with 58 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $9.50.

Most of this provocative consideration of pancreatitis, written by a pathologist and surgeon of the St. Louis group which has contributed so much to our understanding of the disease, is a presentation of possibly relevant observations pertaining to etiology and pathogenesis. Normal and pathologic anatomy and physiology also are discussed at length. These sections of the book contain a remarkable, if somewhat confusing, compendium of reports by many workers, to which the authors have added their own observations, based largely on an analysis of a necropsy series of 163 cases. Reflected in the latter observations are the disadvantages as well as the advantages of retrospective analysis. It may be noted that in only 17 of the 163 cases was the pancreatitis of such severity that it was regarded as the primary cause of death.

For better orientation the reader would do well to read first the conclusion of the volume. The description of pathologic anatomy is excellent, and the photomicrographs are particularly so. Practitioners may be somewhat surprised and disappointed, however, to find that the clinical aspects of pancreatitis receive relatively brief consideration.

The tables are rather complex; the meaning of an occasional sentence is not clear, and at times the grammar and typography are faulty. A few misconceptions and inaccuracies also are apparent. For example, the fecal excretion of nitrogen in patients with sprue usually is not normal, nor is expression of fecal nitrogen content in terms of percentage of the intake of nitrogen very meaningful. Again, only one form of hereditary pancreatitis has been described, and hyperlipemia is not characteristic of this entity.

In spite of these considerations, the authors have gathered together an immense amount of material relating to pancreatitis, and any serious student of the disease will find the book of real interest. The lists of references are especially worthwhile, and the indexes are useful.

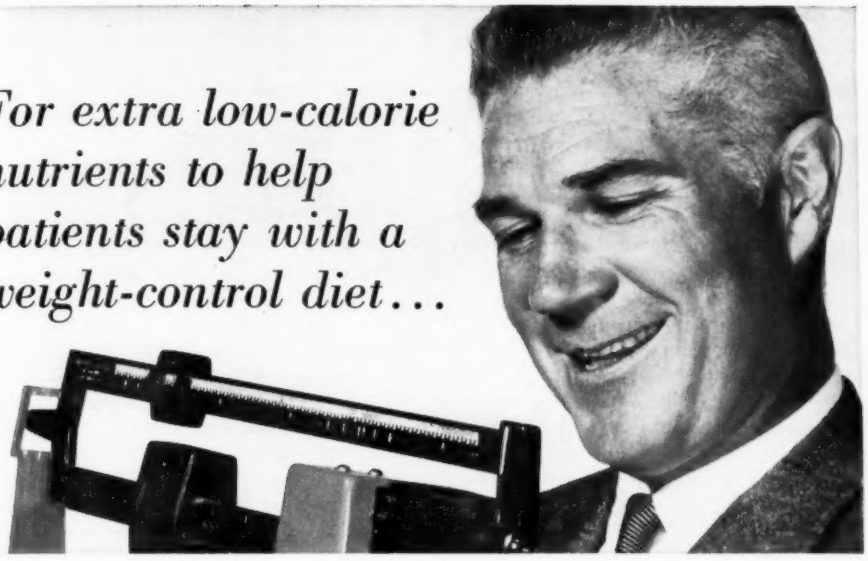
J. B. G.

► THE MOUTH
Its Clinical Appraisal

By A. B. Riffle, D.D.S., Formerly Chief of the Dental Service, Rochester General Hospital, Rochester, New York. 118 pages with 22 illustrations. 1959, J. B. Lippincott Company, Philadelphia and Montreal. $3.50.

Written primarily for the physician, this book describes a step-by-step method for oral examination. It should alert the medical practitioner to some of the problems encountered by his dental colleagues. Many books describe more profoundly the complexities of the oral cavity, but a concise, practical approach to the examination of the mouth, as presented in this interesting text, has been lacking.

(Continued on page A-192)



New *self-enriched* Carnation Instant

25% more protein, calcium, B-vitamins, richer flavor than ordinary nonfat milk

Simple fatigue can discourage patients from staying with weight-control diet. A bonus of sustaining, low-calorie nutrients can help. Carnation Instant can provide such aid.

This new fresh flavor crystal-form nonfat milk can be *self-enriched*—to provide 25% more protein, calcium and B-vitamins than ordinary nonfat milk—and far richer flavor.

The patient simply adds 25% more crystals when mixing. Dissolves instantly in ice-cold water, ready to enjoy.

The chart below shows how this more delicious nonfat milk makes significant contributions, even to the *liberal* Recommended Daily Dietary Allowances of the National Research Council (1958 Revision).

		Protein (Grams)	Calcium (Grams)	Riboflavin (Mg.)	Thiamine (Mg.)
NRC Allowances, Ages 25 to 65	Men	70.0	.8	1.8	1.6-1.3
	Women	58.0	.8	1.5	1.2-1.0
Provided by 1 Qt. 25% self-enriched Carnation Instant		41.3	1.48	2.26	.40

25% self-enriched Carnation Instant
Simply add 1 tablespoon extra Carnation Instant per glass, or 1/3 cup extra Carnation Instant per quart, over regular package directions

Particularly effective are the practical clinical suggestions that are found throughout this small text. The author, an experienced and skillful general practitioner, competently presents a great deal of material, starting with examination technic and concluding with interpretation. The discussions on foci of infection, systemic derangements, and oral health are especially timely.

This book contains six short chapters: (1) examining the mouth, (2) the floor of the mouth, the tongue, stomatitis, pigmentation, foul breath, (3) anesthesia, drugs, diet and nutrition, (4) teeth and remote derangements, (5) orthodontics, and (6) potentially grave criteria.

The reviewer had the impression that he was reading material that the author may well have presented in lectures to medical students and interns.

The author's conclusion best describes the value of this text: "It is satisfying to feel that all of the body's surfaces have been studied—that none have been left to chance. And the mouth, except for the skin, is one of the most readily visible of all.

"The physician who persists in learning will be richly rewarded on the day he finds his first malignant growth 'before it is too late,' and on the days he detects foci of infection in his diabetic, his nephrotic, his rheumatic heart and his arthritic patients. These physicians and dentists will better have justified the trust their patients place in them. And life will be better."

J. A. G.

► THE CARE OF MINOR HAND INJURIES

By Adrian E. Flatt, M.D., Assistant Professor of Orthopedic Surgery, State University of Iowa College of Medicine, Iowa City. 266 pages with 109 illustrations. 1959, The C. V. Mosby Company, St. Louis. $9.50.

The title of this book may be misleading in that minor hand injuries may be defined in several ways. The author's intent is to discuss hand injuries which can be treated properly without admitting the patient to the hospital. The word "minor" implies that the amount of tissue damage is relatively small, facilitating outpatient treatment and not inviting complications.

The first half of the book is a discussion of the general principles of care; the second half applies these principles to specific injuries. Excellent chapters in the first part are devoted to the functional anatomy, surgical technics, and a classification and examination of injuries of the hand. In discussing specific injuries, the author describes injuries to the nail and the pulp; crushing, tendon and joint injuries; fractures; burns; infections, and miscellaneous other effects of trauma.

The text is clear, concise and well written. The reader's time is not taken up with long discussions of various forms of treatment; rather, one form is presented which the author has found to be safe and practical. Throughout the book, extraneous material is kept at a minimum. Conspicuously absent from the book, however, are data from any series of cases treated by the method recommended. Thus, the reader can base his opinion of this method only on the author's general experience and judgment.

The illustrations for the most part are photographs of actual cases, with some line drawings to depict the various anatomic or surgical procedures. The index is complete. An added feature valuable to the interested reader is three pages devoted to a list of recommended texts and articles from the various fields involved in the care of minor hand injuries.

E. W. J.

► DISEASES OF METABOLISM

Edited by Garfield G. Duncan, M.D., Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, with 22 contributors. Ed. 4. 1,104 pages, illustrated. 1959, W. B. Saunders Company, Philadelphia and London. $18.50.

As in previous editions, this new volume contains sections devoted to water balance, vitamins, undernutrition, obesity, glycogen-storage disease, gout, hypoglycemia, diabetes insipidus, melituria, diabetes mellitus in adults and juveniles, diseases of the thyroid glands and kidneys, and the metabolism of protein, carbohydrates, lipids, minerals and porphyrins. Each section has been brought up to date, covering the many developments that have occurred since the third edition was published in 1952.

This text can be highly recommended; it is well written and contains many illustrations and tables. There is a good bibliography at the end of each section.

R. V. R.

(Continued on page A-194)

dust
a major offender

Dust is a principal offender in allergies of the respiratory tract. It cannot be avoided — and the dust-allergic patient requires medical attention. POLARAMINE — the closest to a perfect antihistamine — is the closest to a perfect solution for the problem of the patient suffering from irritating nonseasonal allergens. POLARAMINE offers swift, sure, safe action with these outstanding advantages —

- Therapeutically effective at lower dosages than other antihistamines
- Highest therapeutic index of all antihistamines (3380)
- Fewer side effects than with other antihistamine preparations
- Highly efficacious — a single POLARAMINE REPETAB gives your patient all-day or all-night protection from discomfort of allergic symptoms

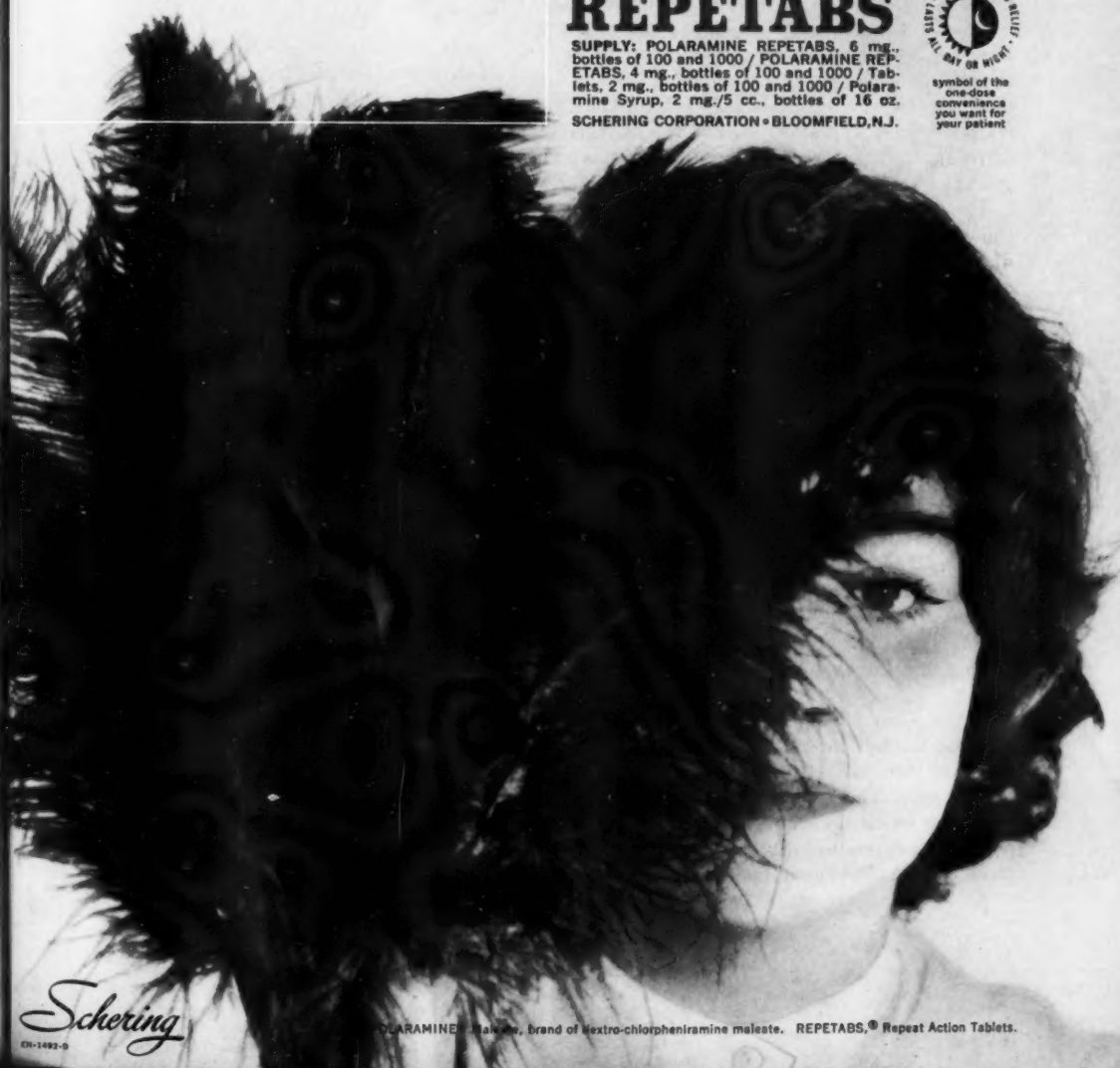
POLARAMINE REPETABS

SUPPLY: POLARAMINE REPETABS, 6 mg., bottles of 100 and 1000 / POLARAMINE REPETABS, 4 mg., bottles of 100 and 1000 / Tablets, 2 mg., bottles of 100 and 1000 / Polaramine Syrup, 2 mg./5 cc., bottles of 16 oz.

SCHERING CORPORATION • BLOOMFIELD, N.J.

PROMPT REPETAB RELIEF · ALL DAY OR NIGHT · SLEEP

symbol of the one-dose convenience you want for your patient



Schering

POLARAMINE® Maleate, brand of dextro-chlorpheniramine maleate. REPETABS,® Repeat Action Tablets.

CH-1492-9

► PREVENTIVE MEDICINE IN WORLD WAR II
Communicable Diseases; Transmitted Chiefly Through Respiratory and Alimentary Tracts

Edited by Ebbe Curtis Hoff, M.D., with 21 contributors. 544 pages, illustrated. 1958, U. S. Government Printing Office, Washington, D. C. $5.50.

Communicable diseases of men and animals have at times inflicted great losses on armies and essential related groups in military efforts throughout the ages. This very fine book is the first of several such volumes presenting the problems of the prevention and control of communicable diseases in the army and in the populations with which the army was in contact during World War II. These problems constituted a major segment of the general mission of the medical department in maintaining the health of the army. Diseases caused by bacteria, spirochetes, rickettsiae, viruses, fungi, protozoa, helminths, ectoparasites and toxins, transmitted from man to man and from animals to man by a wide variety of means and vectors under many variations of global epidemiology, are discussed in this text.

The contributors help to make this text outstanding in nature and presentation. The volume of worthwhile statistics which it contains could not have been gathered from any other source. This book is of great interest, and I recommend it to all physicians interested in gaining a better understanding of the problems of the medical department of the army at all times.

I. P. F.

► THAT THE PATIENT MAY KNOW

By Harry F. Dowling, M.D., Professor of Medicine, and Tom Jones, B.F.A., Emeritus Professor of Medical Illustration, University of Illinois School of Medicine, Chicago. 139 pages, illustrated. 1959, W. B. Saunders Company, Philadelphia and London. $7.50.

The specific function of this unusual volume is to aid doctors in explaining illnesses and disorders to their patients. It is not intended for laymen to read. The book includes a set of simple diagrams which accurately portray proper proportions and relationships of organs and structures. The text is written in simple language, and, if he wishes, the doctor may read to his patients from the text, although Americans in general do not like to be read to, and doctors are not likely to be happy sitting and reading to their patients.

Many illustrated books are already available which physicians may use to explain the causation of diseases, the changes that occur in diseases, and the mechanisms of the body. However, the authors have obviously learned from previous educators and particularly, no doubt, from the extensive experience of Mr. Jones in preparing exhibits for the Museum of Science and Industry in Chicago. Just how useful this book will be remains to be seen. As a contribution to education about health and disease, its value cannot be questioned.

M. F.

► PEDIATRIC NEUROSURGERY

Edited by Ira J. Jackson, M.D., Assistant Professor of Neurosurgery, University of Texas Medical School, Galveston, and Raymond K. Thompson, M.D., Assistant Professor of Neurosurgery, University of Maryland School of Medicine and College of Physicians, Baltimore, with 24 contributors. 564 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $16.50.

The appearance within five years of a second book on pediatric neurosurgery published by the same company attests to the growing interest in this medical specialty. The fact that a fourth of the contributors to this text are not neurosurgeons but are anesthesiologists, neurologists, pediatricians, etc., illustrates the editors' belief that many medical therapists are required to care for children who have neurosurgical disorders.

A wide range of subjects is covered, including anesthesia, electromyography, preoperative and postoperative care, neurologic conditions simulating surgical diseases, trauma, and the various disease entities such as developmental defects, epilepsy, infection and tumors. Thus, the book will be of value to all physicians who deal with children.

Although much variation exists between methods of presenting the different subjects, ranging from a general survey to a detailed review, each presentation is quite adequate and the book as a whole is excellent. Particular mention should be made of the splendid illustrations.

R. G. S.

(Continued on page A-196)

In the menopause...
transition without tears

Milprem promptly relieves emotional distress with lasting control of physical symptoms

Milprem®

Miltown®+conjugated estrogens (equine)

Supplied in two potencies for dosage flexibility:
MILPREM-400, each coated pink tablet contains 400 mg. Miltown (meprobamate) and 0.4 mg. conjugated estrogens (equine).
MILPREM-200, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine).
Both potencies in bottles of 60.

Literature and samples on request.

In minutes, Milprem starts to ease anxiety and depression. It relieves insomnia, relaxes tense muscles; alleviates low back pain and tension headache. As the patient continues on Milprem, the replacement of estrogens checks hot flushes and other physical symptoms.

Easy dosage schedule: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

WALLACE LABORATORIES, *New Brunswick, N. J.*

CMP-9224-C9

► FUNDAMENTALS OF GYNECOLOGY

By Samuel J. Behrman, M.R.C.O.G., Associate Professor of Obstetrics and Gynecology, and John R. G. Gosling, M.D., Assistant Professor of Obstetrics and Gynecology, University of Michigan Medical School, Ann Arbor. 416 pages with 166 illustrations. 1959, Oxford University Press, Inc., New York. $9.50.

The authors of this book have succeeded in compiling in one volume much of the basic material in the field of gynecology, and have presented it in a clear manner with ample illustrations. They have supplemented the text by using photomicrographs and gross histologic pictures side by side to illustrate the conditions described.

Each of the seven major divisions of the book has ample references, and in the conclusion the authors have included a partial list of commercially prepared endocrine products which are used in gynecology.

E. A. B.

► PERIPHERAL VASCULAR DISEASES
An Objective Approach

By Travis Winsor, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine, Los Angeles. 845 pages with 435 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $16.50.

The chapters on anatomy of the vascular system and on dynamics of circulation are well presented in this volume. However, most of the first half of the book is devoted to the discussion of the various technics and to the description of the various instruments which may be utilized in the study of the peripheral circulation. Physicians will find this section rather complete.

Some of the discussion on history taking and on physical examination of the patient seems vague and poorly organized. In the chapter on treatment, the details are not as complete as many practitioners would like them to be.

All of the illustrations are black-and-white drawings. Although these serve well in the chapters on the physics and dynamics of circulation, they are inadequate for showing arteriographic studies, ocular fundi and physical findings.

The general practitioner will find this book cumbersome for everyday use as a reference for the practical management of patients with vascular disease.

J. A. S.

► THE TREATMENT OF DIABETES MELLITUS

By Elliott P. Joslin, M.D., President, Diabetes Foundation, Inc., Howard F. Root, M.D., Physician, New England Deaconess Hospital, Priscilla White, M.D., Assistant Professor of Pediatrics, Tufts University School of Medicine, and Alexander Marble, M.D., Assistant Clinical Professor of Medicine, Harvard Medical School, Boston. Ed. 10. 798 pages, illustrated. 1959, Lea & Febiger, Philadelphia. $16.50.

In the introduction to this edition it is said, "As a result of our 18,055 fatalities, we have gradually accumulated data which compel us to state unequivocally that of those complications which have ravaged our diabetics most can be explained by failure to control the disease. One still reads that retinitis, nephropathy and neuritis bear no relation to control, but our detailed investigation of diabetics who have come under our own supervision proves the contrary." This opinion is shared by the majority of authorities on diabetes mellitus. It has been estimated that there are approximately three million diabetic persons in the United States; hence, it behooves all physicians to be familiar with the proper treatment, as well as the other aspects, of this prevalent disease.

This volume is unsurpassed as a source of information about diabetes mellitus. It has been the standard text in this field since the first edition was published in 1916. The tenth edition continues this tradition. The entire text has been brought up to date. In addition, there is a new section on the orally administered hypoglycemic agents, and the experience at the Joslin Clinic of treating some 3000 diabetic patients with orally administered drugs has been incorporated in the text. In the discussion of metahexamide, one of these hypoglycemic agents, it is stated that no significant untoward effects have been reported. Since this book was published, a number of toxic effects from metahexamide have come to light, and it is likely that this agent will be withdrawn from use.

R. V. R.

(Continued on page A-198)

Traffic: jammed
Car: stalled

Temper: mild
Ulcer: quiet

Here's a man whose ulcer once would have protested strongly—not just at traffic problems—but at the entire gamut of stress to which modern man is subjected.
His physician, aware that *the patient as well as the ulcer* must be treated, has prescribed ALUDROX SA.

eases tension • promotes healing
relieves pain • reduces acid secretion
inhibits gastric motility

ALUDROX® SA

Suspension and Tablets: Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide and Butabarbital, Wyeth

Wyeth®
Philadelphia 1, Pa.

► SYNOPSIS OF OPHTHALMOLOGY

By William H. Havener, M.D., Professor and Chairman, Department of Ophthalmology, Ohio State University College of Medicine, Columbus. 288 pages with 189 illustrations. 1959, The C. V. Mosby Company, St. Louis. $6.75.

Obviously designed to present the practical viewpoint of the ophthalmologist to general practitioners, this pocket-sized book describes common eye diseases and their prevention and care. External examination of the eye is first discussed, followed by chapters on diagnosis and management of eye injuries. Other chapters deal briefly with medical ophthalmology, neuro-ophthalmology, glaucoma, degenerative diseases of the eye, developmental anomalies, and physiology.

This book may very well serve nurses and first-aid workers as a reliable guide in the management of emergency cases until an ophthalmologist can be reached. Definitions are used to clarify technical terms, and a glossary has been added to provide more complete understanding. In the final chapter a strong appeal is made for the application of skill and knowledge in the prevention of blindness.

W. L. B.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers are reviewed more extensively.

A Guide to the Identification of the Genera of Bacteria. By V. B. D. Skerman, Head of the Department of Bacteriology, University of Queensland, Brisbane, Australia. 217 pages, illustrated. 1959, The Williams & Wilkins Company, Baltimore. $5.50.

Recent Advances in Cardiology. By Terence East, D.M., Physician-in-charge of Cardiological Department, King's College Hospital, and Curtis Bain, D.M., Consulting Physician, Harrogate General Hospital, London, England. Ed. 5. 421 pages with 133 illustrations. 1959, Little, Brown & Company, Boston. $10.00.

Home Care for the Emotionally Ill. By Herman S. Schwartz. 232 pages. 1958, Staples Printers Limited, Rochester, Kent, England. Distributed by Sessions Publishers, Elmhurst, New York. $5.00.

The Year Book of Cancer (1958-1959). Compiled and edited by Randolph Lee Clark, Jr., M.D., Director and Surgeon in Chief, and Russell W. Cumley, Ph.D., Director of Publications, University of Texas M.D. Anderson Hospital and Tumor Institute, Houston. 570 pages with 202 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $8.00.

Biochemistry of Blood in Health and Disease. American Lecture Series. By I. Newton Kugelmass, M.D., Consultant to the Departments of Health and Hospitals, New York. 543 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $15.75.

Drug Store Days. By Richard Armour. 184 pages. 1959, McGraw-Hill Book Company, Inc., New York, Toronto and London. $3.50.

Hypertensive Disease; Diagnosis and Treatment. By Sibley W. Hoobler, M.D., Associate Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor. 353 pages. 1959, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. $7.50.

Office Orthopedics. By Lewis Cozen, M.D., Attending Orthopedic Surgeon, Cedars of Lebanon Hospital, Los Angeles. Ed. 3. 430 pages with 321 illustrations. 1959, Lea & Febiger, Philadelphia. $9.50.

An Atlas of Normal Radiographic Anatomy. By Isadore Meschan, M.D., Professor and Director, and R. M. F. Farrer-Meschan, M.D., Research Associate, Department of Radiology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina. Ed. 2. 759 pages with 412 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $16.00.

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Financial Planning
for the Medical Practitioner

A monthly service dealing with the basic problems of increasing your net income and building personal capital . . . *in the face of today's high tax structure*

prepared by the
J. K. LASSER INSTITUTE
for
Postgraduate Medicine

NOVEMBER 1959

The Charitable Life Income Contract - can be useful to the doctor who wishes to couple a charitable donation with his retirement planning. A large number of educational institutions and other tax-exempt organizations now issue these charitable life income contracts. Basically, they call for a gift of cash or property to the charity with the donor retaining a life income interest. On the death of the donor, gift property is owned outright by the charity.

Donor, age 60, has income which reaches the 50% tax bracket. He gives $10,000 to a charity, retaining income from the gift for his life. At his age, the remainder interest in $10,000 which he has given charity produces a charitable deduction of $6,000. In his tax bracket, such deduction reduces his tax bill by $3,000. For practical purposes, real investment in the charitable income contract is $7,000 ($10,000 donation less $3,000 tax saving). If the charity invests the $10,000 in securities yielding 4.5%, income paid to the donor annually during his life will be $450. On a $7,000 investment, an annual return of $450 is the equivalent of a 6.4% yield.

Typically, these charitable life income contracts are issued on one life - that of the donor - but, in the alternative, on the lives of a couple - that of the donor and his spouse. So they can be used not only by the single individual but also by the married person who seeks to provide income for himself and spouse.

Benefits From Charitable Life Income Contracts - can be increased by donating appreciated securities rather than cash. In fact, many of the institutions issuing these contracts seek the property gift. Added benefit to the donor on the gift of appreciated securities results from avoidance of capital gains tax.

Consider a doctor, age 60, who has income which reaches the 50% tax bracket. He holds growth securities which cost him $2,000 but which are now worth $10,000. Sometime before retirement, he will sell such securities and reinvest sales proceeds in stocks which give a greater current dividend return. If he gives the securities to charity in return for a life income arrange-

ment, charitable contribution deduction he secures is based on the market value of the securities given. At his age and in his income tax bracket, the deduction produces current tax savings of $3,000. In addition, he has avoided a capital gains tax of $2,000 which otherwise would have been incurred on sale. On his $10,000 investment in charitable income contract, tax savings run $5,000. So his investment is $5,000. Even if the charity retained gift securities intact and they produced $350 annual income, the donor would be getting a return of 7% based on a $5,000 investment.

Tax-Exempt Life Income - is possible through another variation of the charitable life income contract. Under this variation, the tax-exempt institution receiving appreciated securities, sells the securities and reinvests the sales proceeds in tax-exempt bonds. Income from those bonds is paid to the donor who has retained a life income interest. The Internal Revenue Service has ruled that such tax-exempt interest paid to the donor retains its tax-exempt status in his hands. He need not report such income or pay a tax on it when filing his income tax return.

Consider again the doctor, age 60, who has income which reaches the 50% tax bracket. On his gift of securities which cost him $2,000 but worth $10,000, tax savings reduce his real investment in the charitable income contract to $5,000. If the tax-exempt organization sells the $10,000 gift property and reinvests sales proceeds in tax-exempts yielding 3.5%, the real return to the donor is the equivalent of a 7% tax-exempt return - $350 tax-free interest on $5,000 investment.

What is the value of a 7% tax-exempt return to a doctor after retirement? Even if his taxable income fell to an amount which placed him in the lowest tax bracket, the 7% tax-exempt return would be the equivalent of a taxable return in excess of 8.6%.

* * * * * *

When You Spend Money On A Capital Expenditure - keep supporting records as evidence of the amount spent. There are sound tax reasons for such step. That's so even though the expenditure is for a house to be used solely for living purposes. At some future date, you might sell the house. While you will not be entitled to a tax deduction if sale is at a loss, sale at a profit will result in a current tax unless sales proceeds are reinvested in a new home.

After his children had become adults, a doctor sold his home, purchased many years before. He rented an apartment for

himself and his wife in the building in which his office was located. Taking into account original cost of the home plus capital improvements made to it, the doctor estimated he had a nondeductible loss of $3,000 on sale. However, he had not kept records of all improvements. Result: The Internal Revenue Service claimed he had a $1,000 taxable gain on sale. That was the amount by which sales proceeds exceeded original cost and improvements for which the doctor had records.

Doctor Loses $5,000 Tax Deduction - due to his failure to keep records of capital expenditures relating to his office. The doctor originally practiced in Cleveland. He accepted a position as director of radiology at a medical school of a southern university. While the doctor intended to continue his private practice, it was not practical for him to move his office equipment from Cleveland to the southern city. So he sold such equipment, including valuable X-ray equipment.

To the extent that sales proceeds are less than the tax cost of equipment used in practice, a doctor is entitled to a loss deduction. Tax cost is generally original cost less depreciation. The doctor had failed to keep detailed records relating to X-ray equipment. However, he estimated that his loss on sale was some $5,000 - and he deducted that amount.

While the Internal Revenue Service did not claim that sale of X-ray equipment resulted in a profit, it did deny loss deduction taken by the doctor. A court upheld action taken by the Service. Burden of proof was on the doctor to show the amount of his loss. An estimate without records was not sufficient to permit him loss deduction.

* * * * * *

The Patient Is Free To Choose His Doctor - and if choice requires necessary travel, he's entitled to deduct his travel costs as a medical expense. Over Internal Revenue Service objection, the Tax Court allowed medical expense deduction for travel in this situation.

The patient, who was under doctor's care in New York, moved from New York to California. After changing his residence, the patient made annual trips back to New York for medical "check ups." His trips were primarily for medical reasons although the patient renewed acquaintance with old friends, attended shows, etc., while in New York. The Tax Court, finding that the trips were for medical purposes, allowed the patient to deduct his travel costs and also living expenses incurred in making the trip. The tax law doesn't require a taxpayer to find a local doctor to treat him under these circumstances.

If Your Son Worked During The Summer Vacation - ask him if he got a form W-2 from his employer. This is the form which shows the amount of an employe's earnings and amount of tax withheld on such earnings. Some companies, knowing junior will not be working once school starts, automatically include a W-2 with his final paycheck - and often junior misplaces it. If junior earned more than $600, he's required to file a tax return. Regardless of his earnings, he'll probably still be your dependent and be entitled to some tax refund of withholding tax. But to file return and get refund, he'll need his W-2. He can, of course, get a new one from employer if he loses or misplaces it. However, it saves time, avoids annoyance for all concerned - if he realizes importance of a W-2 which he may have already received or will be receiving by January.

Action Taken By The American Red Cross - could be of interest to the doctor who is employed by a tax-exempt organization, e.g., teaches in a medical school, does research work, etc. Within certain limits, premiums paid by an exempt organization on a retirement annuity for an employe are not taxed currently to the employe. Tax is deferred until the employe receives annuity payments at time of retirement. Thus, it is possible to set up a retirement program for such employes without current tax.

However, premium payment by a tax-exempt organization is a form of salary increase to an employe. What if the organization doesn't have the funds for such premiums? The employe might arrange for a reduction in compensation with the salary cut invested by the employer in an annuity. Apparently, that's what the Red Cross is doing. How does the employe benefit when he agrees to compensation reduction to be invested in an annuity? This example was cited.

A 35-year employe who forgoes $10 every two weeks would get a retirement benefit of more than $75 a month at age 65. If the same employe in the 30% tax bracket invested directly in an annuity the amount he keeps after taxes on $10 income, the annuity would produce less than $55 a month for him at age 65.

If A Casualty Does Extensive Damage To Your Residence - it pays to bring in an experienced and reliable appraiser to fix loss in value. His appraisal can be important in fixing the amount of your tax deduction for casualty loss. Recently, the Service so conceded when appraisal is made by an experienced appraiser familiar with property values and your neighborhood.

Added tax point: The fee you pay the appraiser also is deductible.

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DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Sept. 1—In the afternoon to meet our guests from abroad, including Muniwar Ali from Karachi, president of the Pakistanian Medical Association; Dr. Guido Bossa, professor of medicine in Naples; Dr. O. Garcia Loselle of Lima, Peru; Dr. Gino Frontali, professor of pediatrics in Rome; Dr. Sol Wand of Birmingham, England, chairman of the Council of the British Medical Association; Dr. J. McCrie from Sheffield, England, professor of medicine, and Dr. A. Sison and his lady of Manila.

All of us to visit the exhibit of rare medical books from the Herbert McLean Evans collection, which has been purchased for the University of Chicago. Next to the Quadrangle Club for hors d'oeuvres and cocktails. Here came Dr. Morris Friedell with the radiologists Baker and Sammet and also Walter Palmer, accompanied by Sir George Pickering, Regius professor of medicine at Oxford, and Dr. Edward George Hayres, dean of the medical school and professor of therapeutics at the University of Otago in Dunedin, New Zealand. Thereafter, many come to dine with us, and this was a joyous occasion.

Sept. 2—At the early hour of 8:30 A.M. to answer questions on Don McNeill's program and then to the Crerar Library to read for several manuscripts now in preparation. In the evening with Charles Lawrence to the Michael Reese Hospital, where Louis Katz introduced Sir George Pickering, who spoke of his studies which prove the hereditary characteristics of essential hypertension.

Sept. 3—To luncheon at the Tavern Club, where came Bossa of Naples, Wand of Birmingham, and Prywes of Israel, and we discussed problems of medical education. As we walked to view the city from high up in the building, we saw Austin Smith, Mallon and Tyler of Australia also at lunch. In the afternoon for the beginning of my checkup with Charles Lawrence, and he found everything well except for an enlargement of the appetite.

Sept. 4—Early to the final session of the Second World Conference on Medical Education, and found many experts busily summarizing the activities of the previous days. In the afternoon again at the desk reading new books and delving further into the life of Christian Fenger.

Sept. 6—At noon came Leon Unger and his lady to brunch. Afterward, all of us to see the White Sox play and immediately realized how much finer is the game when witnessed at the field than when seen on television. In the evening to dine at the Standard Club and then to see "Anatomy of a Murder," a motion picture with much to say about rape, spermatogenesis, contraception and similar subjects.

Sept. 7—To play at golf with M. Goldblatt and A. Altheimer in 95° heat, and then to recover by going early to bed.

Sept. 9—To see my medico and converse with him, finding that more of the findings were what they should be. At noon to the Chicago Heart Association, and there assembled the committee on the home care program, which is suddenly stymied by the conservatism of the bureaucracy. In the evening to the home of Rhodes on Lake Shore Drive, where came a group of young people, including Welber, Miss Peyton and Brooks, to give readings and tape recordings of a play by Brecht called "Mother Courage." His plays like "The Threepenny Opera" and "Soldier Schweik" have universal appeal.

Sept. 10—By the early morning plane to Newark, reading en route the book by Niven Bush called "California Street," which is a great story of the newspaper business as it was around San Francisco. In Newark to dine in the airport cafe with Landshoff, who wanted some editorial and business opinions concerning works to be published. Then driving with Charles Haney to Toms River and spoke there in the armory to some 500 people, the largest assemblage ever in Toms River, and the talk was of their new hospital. Allerdice presided and we talked about people we knew in New Jersey, in particular former Governor Al Driscoll, who had made Allerdice head of the Civil Service Commission. Then driving back to New York and arriving at the Waldorf at midnight.

Sept. 11—At 9 A.M. came Bill White to talk of our new projects in publishing. Afterward, conferred with Paul Warwick, Wachtel, Malloy and Fred Baldwin for some two hours and observed the excitement of getting Warwick off to Europe. Next to luncheon

(Continued on page A-216)

with Max Geffen at the Radio City Club and saw there Alfred Sloan, who had just given a great sum for the education of Negro physicians. Thereafter to Doubleday to get some new books, in particular the plays of Brecht, and talked with Doug Black about publishing and decorations. By the afternoon VIP flight on Capital back to Chicago and spent the evening catching up with the mail.

Sept. 12—At the desk with my scrivening and read the play "Mother Courage," which I found modernistic, and thought it hardly likely to succeed with an American audience. In the afternoon to the dedication of the French, Dutch, Spanish and Danish rooms in the Hall of Fame for Surgery and was thrilled by observing the gifts which Napoleon had given to his surgeon Baron de Larrey and also a wonderful bust of Ramón y Cajal. Thereafter to dine at the Whitehall, and met en route Sam and Dorothy Salinger just come from Palm Springs.

Sept. 13—All this day with the family and in the evening all of us to eat great stacks of perch at Phil Smidt's.

Sept. 14—At the desk for many conferences with men who have come from far and wide to attend the meeting of the International College of Surgeons. Read Pritchard's "Aids to Neurology," and thought it wonderful that a medical book should be printed so compactly and at such low cost.

Sept. 15—To the Palmer House, where some hundreds of surgeons assembled, and old Pepys opened the meeting with an address on the life of the great Christian Fenger, the pathologist and surgeon who was the teacher of Hektoen, Billings, Murphy and, in fact, most of the great in Chicago's medical history. Thereafter for a conference with the workers of the City of Hope, and then to the Palmer House for a luncheon which Max Thorek tendered to medical leaders of France, Sweden and many other nations. At night to the Tavern Club, where came to dinner our old friend Manuel Astor of Puerto Rico and also Dr. Winney of Newcastle upon Tyne. There was a fine dinner and much conversation of changing methods of medical services, with leading questions asked by Barbara and Morris Friedell.

Sept. 16—At noon to Stouffer's to speak on the various problems of accident prevention to some 75 government employees who constitute what is called the Federal Safety Council. Here were many workers of the post office, the FBI, the internal revenue and the social security divisions, and altogether a most pleasant occasion at which Dr. Stucker introduced old Pepys.

In the evening to the great dinner of the International College of Surgeons, held in the Grand Ballroom of the Palmer House, with about the greatest attendance I have ever seen in this great hall. Dr. Ed Compere, president, made the opening address. Old Pepys presided as toastmaster; Dr. Ross McIntire presented citations, and Dr. Ebersole of the navy, who was on the Sea Wolf (the submarine that was underwater for some 30 days), told of life aboard the submarine. The audience sat enthralled to hear how people live when confined in such a tiny space.

Here were the daughters of John B. Murphy as guests of O'Donoghue. Here also was Vice-Admiral Bart Hogan, with whom I sat in the Empire Room more than 20 years ago after he had been blown from the deck of a battleship; Admiral James of Great Lakes and many others of the navy brass; and General Arnolt of the Fifth Army. At 11:30 departed for home well content with a great occasion.

Sept. 17—To the Standard Club for lunch to meet with the businessmen's committee for the great "Salute to Medical Research," and Dr. Karl Meyer was elected general chairman. Chatted here with Bill Sutherland of the *Chicago American*, Art Snider of the *Daily News*, and others who covered this meeting. At 2:30 P.M. to meet with James Cunningham and the advisory committee for the Cook County Commissioners to discuss the necessary improvements to the County Hospital. Late in the afternoon with Rabbi Louis Mann and Ruth to the home of the Kirsners, where was a fine buffet supper honoring the birthday of our host, and all the evening was joyful.

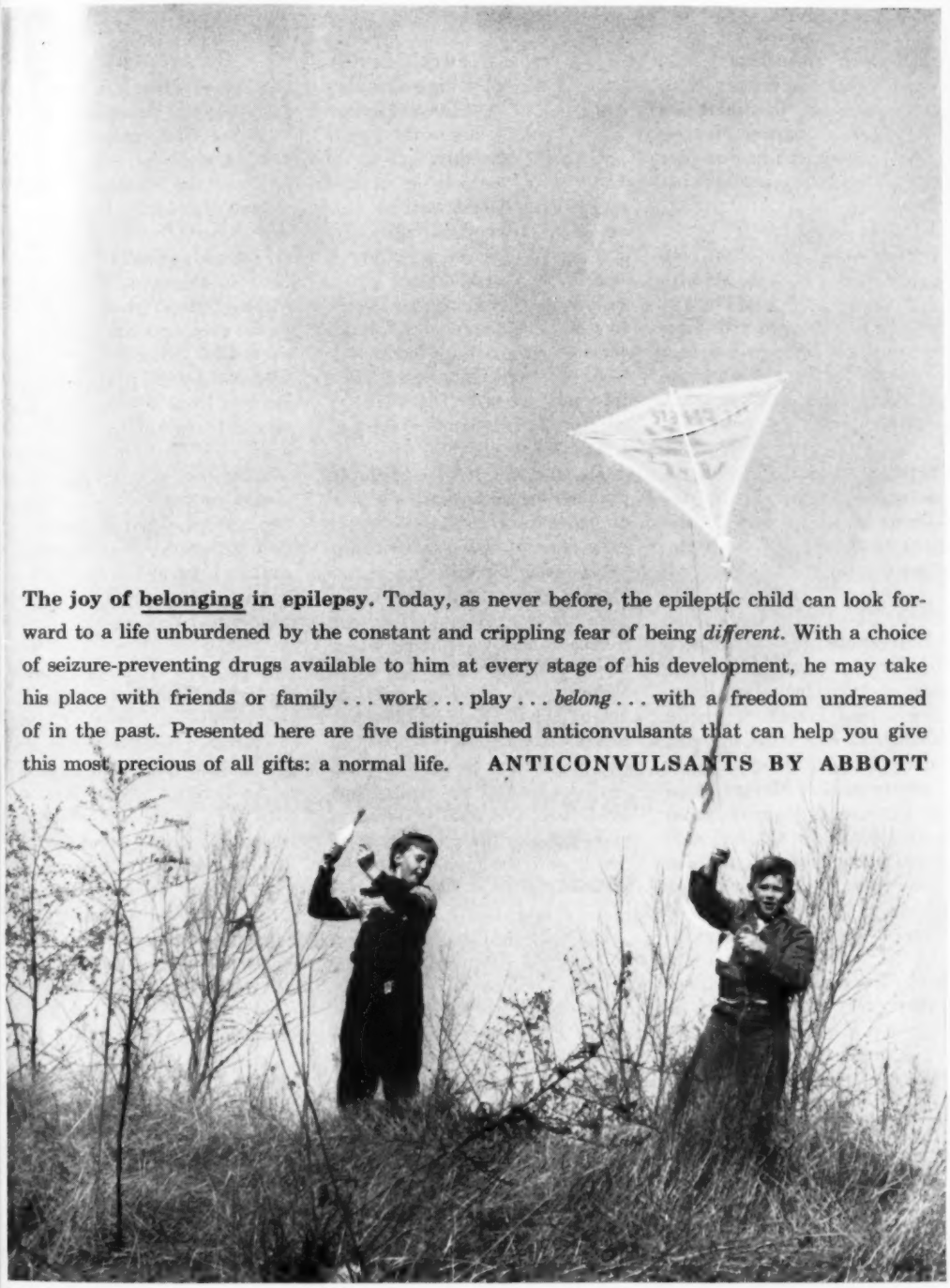
Sept. 18—All this day engaged in meetings with Charles Lawrence and Baker, the roentgenologist, who came forth with marvelous reproductions of my

(Continued on page A-218)

Psychic or Physical

"And now according to Crout and Sjerdsma . . . the banana turns out to be a donor of serotonin, that amphibaric, double-headed Janus of smooth muscle, principle of the carcinoid, and Hermes of tranquilizers. Few suspected that the ingestion of this decorator of breakfast cereal might significantly aid the control of their mental homeostasis, or perhaps even compete with the analyst's couch at 5 cents'a throw."—*New England Journal of Medicine.*

* * *



The joy of belonging in epilepsy. Today, as never before, the epileptic child can look forward to a life unburdened by the constant and crippling fear of being *different*. With a choice of seizure-preventing drugs available to him at every stage of his development, he may take his place with friends or family . . . work . . . play . . . *belong* . . . with a freedom undreamed of in the past. Presented here are five distinguished anticonvulsants that can help you give this most precious of all gifts: a normal life. **ANTICONVULSANTS BY ABBOTT**

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interior and after this travail pronounced me physically satisfactory. At night with Stuart Leterman, Rabbi Mann and Mistress Pepys to see the White Sox play against Detroit to a packed house in Comiskey Park.

Sept. 19—The end of the golfing season draws nigh, so with Mistress Pepys to Ravisloe and enjoyed the opportunity to play, but found the weather had suddenly burned great patches in the fairways, which is likely to mean more assessments next year.

Sept. 20—All the day at the desk, reading and preparing for addresses to be given in Minneapolis. Betweentimes, observing the performances at baseball.

Sept. 21—On the early plane to Minneapolis and at luncheon with Teresa Cohen and Sylvia Covet at the Dyckman Hotel, where a new French cuisine is available. Cheese canalone particularly tempted the appetite. In the afternoon come Marcus Alexis and Professor Upgren from Macalester College to confer on medical economics. At night to speak on the future of medicine to members of the Academy of General Practice, who had invited the specialists as their guests. Here meeting again Dean Howard from the University of Minnesota Medical School; Dr. Guarda, who is en route to Korea for some years of administration, and Moses Barron, who looks and acts as young as ever he did. Here also were the officers of the Minnesota State Medical Association and the Hennepin County Medical Society, and Mr. Cook had arranged a great occasion.

Sept. 22—Early to the offices of POSTGRADUATE MEDICINE to confer with Victor Lowrie, Editor Covet and others. Thereafter to the Oak Ridge Country Club, where some 500 ladies had assembled to hear old Pepys speak on "The three phases of Eve," during which he referred especially to some various concepts of our modern ladies. Today the average young housewife looks like a girl, dresses like a boy, thinks like a man, and works like a dog. Old Pepys reminded them that women are like money—if you don't keep them busy, they lose interest. The auxiliary of the Mount Sinai Hospital, which Mistress Pepys helped organize in 1950, has so developed that the original membership of 50 has grown to 2,185. So the program was completed with the presentation of pins, and it was altogether an exciting occasion.

In the evening to dine with Teresa Cohen at her home, where came also Jay Phillips, Owen Wangensteen, Mal Herz and their ladies, Sylvia Covet and the Gilmores (Mrs. Gilmore is president of the Mount Sinai Hospital auxiliary). And we had a fine feast, with everyone pitching in to help make the crepes suzette, which were the high light of the occasion.

Sept. 23—At the desk, after a quick flight from Minneapolis, and read with excitement Nathan Kline's book on "Psychopharmacology Frontiers," and this is in truth the forefront of modern pharmacologic investigation. In the afternoon came Ilza Veith to discuss the plans for the meetings on medical history. Then with Mistress Pepys to Cog-Hill, where the staff of the Jackson Park Hospital held their *fiesta*, and Elmer Gertz had arranged it most charmingly. Old Pepys spoke, and some 75 members of the staff who drew lucky numbers marched forward to receive their prizes.

Sept. 24—At noon to the Blackstone Hotel, where some 300 gorgeous ladies assembled to help the Children's Aid of La Rabida, and here were Ralph Bellamy with his lovely wife, and we talked a bit of former times, and Albert Pick made a quick speech and took off for Las Vegas. Next to the open house of the Chicago Heart Association and in the evening with Justin to the Press Club, where Len O'Connor moderated and Irv Kupcinet and Herbert Lyon discussed the technics of preparing a gossip column. Old Pepys asked them whether they received more complaints or thanks for publishing the news of a VIP's illness, and they agreed that this was touchy stuff and that it was best to refer to all the coronaries as "a slight heart attack."

Sept. 25—At noon to luncheon with Janet Kern, who does the radio column for the *Chicago American*. Next to visit with Charles Lawrence and after that to the Tavern Club for some talk with Dr. Norman DeNosaquo, who is concerned about the need for investigating the nostrums. At night to the Pearson to dine with the Howard Wolfsons, who put on a glorious feast, and after that at bridge with Hirschfield, Wilhartz and George Lurey, and old Pepys was fortunate to lose only one simoleon.

Sept. 26—To the Standard Club for a luncheon with Friedell and Sam Hoffman, and after that viewing the baseball game.

Sept. 27—Finished "The Lotus Eaters," by Gerald Green, and found it a contrived work shooting at a dozen social problems, with an intellectual heroine who is too easily seduced, but

(Continued on page A-220)

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the satire on the frivolities and stupidities of Miami Beach and on the weaknesses of television is sufficient to make the book worth the time it takes. So out to Highland Park for a luncheon with Justin's family at a Marshall Field restaurant called the Crab Apple, and this series of restaurants equals the finest seen abroad. In the evening to dine with all the Marks family at the Oasis, which is a Fred Harvey restaurant situated across the top of a toll road.

Sept. 28—To Chattanooga by the morning plane and met by Dr. Sheridan. So to the Read House, which is full of comforts and conveniences, in particular an electric device in the bathroom which is provided with two coffee cups, instant coffee, instant cream and "instant" sugar, and the push of a button makes hot water in a few seconds so that coffee is always available. Here was the meeting of the Tennessee Valley Medical Assembly, at which Dr. Hartung presided and papers on hernia by Chester Guy and on hypnosis by Erickson were given to a packed house in the ballroom. At noon to luncheon with the chapter of the International College of Surgeons, to which came some 50 surgeons to hear Ross McIntire speak on the subject of rehabilitation.

In the evening to speak at the great banquet on "The changing social order," and the audience filled several rooms. Here were Allen and Love of the Mayo Clinic; Askey and Kegel of Los Angeles; my friend Lee Hill of Des Moines, who told me of the new mental health addition to the hospital provided by Blank; George Eaton of Baltimore, and Juan A. Del Regato of Colorado Springs. Greeted also Hurxthal and Harken of Boston, so that it was like a special session of the medical Chautauqua and banquet circuit.

Sept. 29—To the early plane for Chicago and somewhat delayed by a loose spark plug in the engine, arriving in the afternoon. Then to the Drake Hotel, where Jessica McLaughlin Greengard presided and old Pepys was drafted to sit in a panel with feature editors and food editors of various publications. Then with the Friedells for dinner at Andy's Epicurean Cafe.

Sept. 30—Early to participate in Don McNeill's Breakfast Club and submitted to the usual curbstone consultations, for the tenor had a painful disk, Mimi Benzel complained of sciatica, and Anita Bryant was away having her tonsils removed in her home town of Tulsa. And the rest of the day at the desk catching up with the problems of the moment.

The Medical Muse

RICHARD ARMOUR

REMEMBER LISTER

That wicked germ, Staphylococcus,
Is apt to lurk about and mock us
And, having swum through deadly oceans
Of chemotherapeutic potions,
Spring up, with vim, from some direction
And cause a troublesome infection.

It may seem odd, may seem like perjury,
May seem old-fashioned, yet in surgery
The only sure way, still, of drubbing
Staphylococcus is by scrubbing,
For, like my little son and daughter,
What makes Staph flee is soap and water.

NURSE, HAND ME MY OIL CAN

Will automation do away
With doctors, also, some fine day?
Will patients then, when they are ill,
Just press a button for a pill?

Will metal monsters cut the skin
With scalpels, probe around within,
And having done what's needed, then
Stitch up the patient once again?

If things should come to such a pass,
With doctors mostly steel or brass,
There should be little cause for rue,
For patients will be robots too.